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THE IMPACT OF LIFESTYLE AND CARDIOVASCULAR RISK FACTORS IN MIDLIFE ON THE HEALTH-RELATED QUALITY OF LIFE AMONG OLD MEN

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ACADEMIC DISSERTATION

To be presented with the permission of the Medical Faculty of the University of Helsinki for public examination in Auditorium XII in the Main Building of the University of Helsinki, Unioninkatu 34, on April 9, 2010, at 12 noon.

ISBN 978-952-92-6998-3
ISBN 978-952-10-6130-1 (PDF)

http://ethesis.helsinki.fi
Yliopistopaino
Helsinki 2010

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1 ABSTRACT

Prevention of cardiovascular diseases is known to postpone death, but in an aging society it is important to ensure that those who live longer are neither disabled nor suffering an inferior quality of life. It is essential both from the point of view of the aging individual as well as that of society that any individual should enjoy a good physical, mental and social quality of life during these additional years. Consequently, reports of the personal experience of how individuals consider the impact of disability or illness on their ability to function or their sense of well-being has become a vital addition to the overall assessment made of their health.

The studies presented in this thesis investigated the impact of modifiable risk factors, all of which affect cardiovascular health in the long term, on mortality and health-related quality of life (HRQoL). The hypothesis was that since much of the illness and disability in old age is related to cardiovascular risk factors in midlife, the existence of lower risk factors not only postpones death but also reduces disability and infirmity and thus provides a better quality of life in old age.

1.1 DATA AND METHODS

The data is based on the all male cohort of the Helsinki Businessmen Study. This cohort, originally of 3.490 men born between 1919 and 1934 has been followed since the 1960's. The socioeconomic status of the participants is similar, since all the men were working in leading positions. Extensive baseline examinations were conducted among 2.375 of the men in 1974 when their mean age was 48 and at this time the health, medication and cardiovascular risk factors of the participants were observed. Among them a subcohort was established of 1.815 men who, in 1974, were healthy and without chronic diseases or in need of medication. These three stages: the initial examinations in the 1960's, examinations in 1974 and the identification of a healthy subcohort in 1974, constitute the basis for the substudies in this thesis. In 2000, at the mean age of 73, the HRQoL of the survivors of the original cohort was examined using the RAND-36 mailed questionnaire (n=1.864). RAND-36, along with the equivalent SF-36, is the world's most widely used means of assessing generic health. The response rate was generally over 90% for the core questions. In 2002, a questionnaire among 633 men investigated their mental well-being. Mortality was retrieved from national registers in 2000 and 2002.

For the six substudies of this thesis, the impact of four different modifiable cardiovascular risk factors (weight gain, cholesterol, alcohol and smoking) on the HRQoL in old age was studied both independently and in combination. The

follow-up time for these studies varies from 26 up to 39 years. Mortality is reported separately or included in the RAND-36 scores for HRQoL.

1.2 RESULTS

Elevated levels of all the risk factors examined (weight gain, alcohol, cholesterol and smoking) among the participants in midlife led to a diminished life expectancy. This was the case when the risk factors were examined either individually or in combination.

Of the independent risk factors, weight gain in midlife increased mortality only in the highest weight gain group of over 15 kgs. Among survivors, lower weight gain was associated with better HRQoL. Men with no weight gain in midlife had consistently the best quality of life in old age, both physically and mentally.

Higher levels of serum cholesterol in middle age indicated both an earlier mortality and a decline in the physical component of HRQoL in a dose-response manner during the 39-year follow-up. The mental component of HRQoL did not differ between the lower and higher baseline cholesterol groups (serum cholesterol ≤ 5.0 or > 5.0 mmol/L).

The findings showed that mortality was significantly higher in the highest baseline category of reported mean alcohol consumption (≥ 5 drinks/day), but fairly comparable in abstainers and moderate drinkers during the 29-year follow-up. When HRQoL in old age was accounted for mortality by imputing deaths in the RAND-36 scores it emerged that men with the highest alcohol consumption in midlife clearly had poorer physical and mental health in old age, but the HRQoL of abstainers and those who drank alcohol in moderation were comparatively similar.

The amount of cigarette smoking in midlife was shown to have had a quantitative related effect on both mortality and HRQoL in old age during the 26 year follow-up. The men smoking over 20 cigarettes daily in middle age lost about 10 years of their life-expectancy. Meanwhile, the physical functioning of surviving heavy smokers in old age was similar to men 10 years older in the general population.

The impact of clustered cardiovascular risk factors was examined by comparing two subcohorts of men who were healthy in 1974, but with different baseline risk factor status. The men with low risk had a 50 % lower mortality during the 29-years follow-up. Their RAND-36 scores for the physical quality of life in old age were significantly better. The mental scores of RAND-36 were not statistically different, but the 2002 questionnaire examining psychological well-being further indicated significantly better mental health among the low-risk group.

1.3 CONCLUSIONS

The thesis of these studies is that favorable levels of cardiovascular risk factors earlier in life can postpone both death and the onset of disability and can also support well-being in old age. This hypothesis was examined in a homogenous cohort of men whose personal health and quality of life were assessed from middle age until survivors reached a mean age of 73. The results indicate that different risk factor levels in midlife have a meaningful impact on the quality of these extra years. Leading a healthy lifestyle improves both survival and the quality of life.

2 TIIVISTELMÄ (SUMMARY IN FINNISH)

Kehittyneiden maiden väestön odotettavissa oleva elinikä on lisääntynyt erityisesti sydän- ja verisuonisairauksien vähentymisen ansiosta. Yhä useammat saavat elää täyden elinkaaren, samalla kun yli 65-vuotiaiden osuus väestössä tulee lisääntymään vuosina 2010–2030. Suomessa 80 % miehistä elää yli 65-vuotiaaksi, ja lähes puolet heistä saavuttaa 80 vuoden iän.

Pitempään eläminen ei kuitenkaan automaattisesti takaa parempaa elämänlaatua, koska tällöin saattaa jäädä enemmän aikaa erilaisten pitkäaikaissairauksien aiheuttamalle toimintakyvyn alenemiselle. Keskeinen kysymys on, kannattaako elinikää pyrkiä pidentämään, jos se johtaa suureen määrään toimintakyvyttömiä vanhuksia, joiden oma elämänlaatu on huono, ja joiden hoito käy kansataloudelle kestämättömäksi. Tämän selvittämiseksi on arvioitava muitakin tekijöitä kuin kuolleisuutta ja sairastavuutta.

Henkilön oma arvio hyvinvoinnistaan onkin tullut yhä tärkeämmäksi mittariksi perinteisten päätetapahtumien rinnalle sekä yksilön, että yhteiskunnan näkökulmasta. Elämänlaadun luotettava mittaaminen on kuitenkin tullut mahdolliseksi vasta validoitujen kysymyssarjojen kuten RAND-36, tultua laajempaan käyttöön.

Viimeisten elinvuosien elämänlaatuun vaikuttavia tekijöitä arvioitaessa on myös kuolleisuus otettava huomioon: poikkileikkaustutkimuksessa saadaan tietoa vain eloonjääneiltä, usein siis jo pitkälle valikoituneesta, terveemmästä joukosta. Seurantatutkimuksen tuloksissa tämä voidaan ottaa paremmin huomioon. Toisaalta verisuonisairauksien riskitekijät, kuten esimerkiksi tupakointi, alkavat vaikuttaa jo nuorella iällä, saattaen siten vaikuttaa eri ryhmien terveyseroihin jo keski-iässä, ennen seurantatutkimuksen alkua.

2.1 HELSINGIN JOHTAJATUTKIMUS (HELSINKI BUSINESSMEN STUDY)

Tämän väitöskirjan osatutkimusten tavoitteena oli selvittää, miten elintavat ja keski-iässä esiintyvät tavallisimmat sydän- ja verisuonisairauksien riskitekijät vaikuttavat elämänlaatuun vanhalla iällä.

Tulokset perustuvat ns. Helsingin Johtajatutkimuksen aineistoon. Helsingin Johtajatutkimuksessa on seurattu 1919–1934 syntyneiden 3 490 suomalaisen miehen terveydentilaa 1960-luvulta nykypäiviin saakka. He kuuluivat ylimpään sosiaaliryhmään.

Vuonna 1974, jolloin kohortin keski-ikä oli 48 vuotta, miehille suoritettiin laajat elintapoihin ja terveyteen liittyvät selvitykset, joiden perusteella voitiin valita seurantaan ne henkilöt, jotka olivat terveitä ja joilla ei ollut säännöllisiä lääkityksiä, mutta joiden riskitekijätasot vaihtelivat matalasta korkeaan.

Vuonna 2000, jolloin elossa olevien keski-ikä oli 73 vuotta, tutkittaville lähetettiin kirjekysely, jolla selvitettiin elintapoja (mm liikunta, tupakointi ja alkoholinkäyttö), sekä sairauksia ja niiden riskitekijöitä. Kyselyyn sisältyi myös terveyteen liittyvän elämänlaadun mittari RAND-36 (RAND 36-Item Health Survey 1.0, yhteneväinen SF-36® -mittarin kanssa), jonka suomenkielinen versio on validoitu suomalaiselle väestölle.

2002–2003 tutkittaville lähetettiin lisäksi henkistä hyvinvointia tarkemmin kartoittava kirjekysely. Tutkimuskohortin kuolleisuutta on seurattu Väestörekisteristä 31.12.2002 saakka.

Tutkimuksen vahvuuksina ovat pitkä seuranta-aika, sosioekonomisesti homogeeninen tutkimusjoukko, sekä laajat lähtövaiheen perustiedot, jotka mahdollistavat sekoittavien tekijöiden huomioimisen tuloksissa. Kohortin valikoituneisuuden vuoksi esitettyjen tulosten soveltamiseen eri-ikäisiin tai eri sosiaaliluokkaan kuuluviin miehiin, ja erityisesti naisiin on kuitenkin suhtauduttava varauksellisesti.

2.2 OSATUTKIMUS I: VARHAISESSA KESKI-IÄSSÄ TAPAHTUNEEN PAINONNOUSUN YHTEYS KUOLLEISUUTEEN JA MYÖHEMMÄN IÄN ELÄMÄNLAATUUN.

Väitöskirjan I osatutkimuksessa selvitettiin varhaisessa keski-iässä tapahtuneen painonmuutoksen yhteyttä myöhemmän iän elämänlaatuun. Kohortti jaettiin viiteen eri ryhmään 25 ikävuodesta vuoteen 1974 (keski-ikä 46 vuotta) tapahtuneen painonnousun mukaan. Tulosten mukaan vain suurin painonnousu, yli 15 kg, ennusti lisääntynyttä kuolleisuutta seuranta-aikana. Sen sijaan vanhuusiän elämänlaatu

oli suorassa yhteydessä aiemman painonmuutoksen suuruuteen 26 vuoden seurannassa: miehillä, joiden paino ei noussut keski-iässä, oli paras elämänlaatu vanhuksena, ja mitä enemmän paino oli noussut, sitä huonompi sekä fyysinen että psyykkinen elämänlaatu oli seurannassa kaikilla RAND-36 mittarin kahdeksalla osa-asteikolla. Erityisen selvästi elämänlaadun erot tulivat esiin fyysisen toimintakyvyn ja fyysisen roolitoiminnan asteikoilla, heijastaen toiminnanvajavuuden (disability) kehittymistä.

2.3 OSATUTKIMUS II: KESKI-IÄN KOLESTEROLITASON YHTEYS KUOLLEISUUTEEN JA MYÖHEMMÄN IÄN ELÄMÄNLAATUUN.

Osatutkimuksessa II tutkittiin keski-iän (keskimäärin 38 vuoden iässä) kolesterolitason yhteyttä kuolleisuuteen ja vanhuusiän elämänlaatuun. 39 vuoden seuranta oli aloitettu ennen nykyaikaisten kolesterolia alentavien lääkkeiden käyttöön tuloa. Perusvaiheen kolesterolitasolla oli suora yhteys kuolleisuuteen seuranta-aikana: Kuolleisuus lisääntyi noin 11 % jokaista 1 mmol/L kolesterolitason nousua kohden. Myös elämänlaatu huononi korkeamman kolesterolitason myötä: Keski-iässä alimman kolesterolitason (alle 5,0 mmol/L) omaavien miesten fyysinen elämänlaatu oli vanhemmalla iällä parhain kaikilla RAND-36 mittarin asteikoilla verrattuna tätä korkeamman kolesterolitason omaaviin miehiin. Fyysisen terveydentilan kokoomamuuttuja oli erittäin merkitsevästi parempi pienimmän kolesterolitason ryhmässä. Tämä piste-ero vastaa toiminnanvajavuuden siirtymistä noin kolmella vuodella eteenpäin niiden hyväksi, joiden kolesterolitaso keski-iässä oli matala. Psyykkisen terveydentilan kokoomamuuttujan pisteet sen sijaan olivat lähes identtiset. Lähtövaiheen matalaan kolesterolitasoon ei siis liittynyt psyykkisen elämänlaadun heikentymistä vanhalla iällä – mutta ei myöskään selkeää paranemista.

2.4 OSATUTKIMUS III: KESKI-IÄSSÄ TAPAHTUNEEN ALKOHOLINKÄYTÖN YHTEYS KUOLLEISUUTEEN JA VANHEMMAN IÄN ELÄMÄNLAATUUN.

Osatutkimus III selvitti keski-iässä tapahtuvan alkoholin käytön yhteyttä kuolleisuuteen ja myöhemmän iän elämänlaatuun. Helsingin Johtajatutkimuksen ryhmän sosiaalinen homogeenisyys vähentää sosioekonomisten erojen aiheuttamaa virhevaikutusta. Myös poikkeuksellisen pitkä seuranta-aika, 29 vuotta, lisää tulosten luotettavuutta, joskin muutokset tutkittavien alkoholin käytössä voivat olla sekoittava tekijä pitkässä seurannassa. Tutkimukseen osallistuneet miehet jaettiin keski-iässä raportoidun alkoholin käyttömäärän perusteella kolmeen

ryhmään: nolla-käyttäjät, kohtuukäyttäjät (1-3 annosta/päivä) ja suurkuluttajat (yli 3 annosta/päivä). 29-vuoden seurannassa kuolleisuus oli samaa suuruusluokkaa sekä nollakäyttäjillä (25 %) kuin kohtuukäyttäjilläkin (27 %), sen sijaan selvästi korkeampi (38 %) suurkuluttajien kohdalla. Sydän- ja verisuonisairauksista johtuvassa kuolleisuudessa ei sen sijaan ollut eroa eri ryhmien välillä. Ryhmien välillä ei ollut selkeitä eroja elämänlaadussa vanhalla iällä, ei fyysisen eikä psyykkisen komponentin osalta. Sen sijaan, kun myös kuolleet huomioitiin elämänlaatua laskettaessa (heikkona elämänlaatuna), oli elämänlaatu suurkuluttajien ryhmässä selvästi huonompi kuin alkoholia vähemmän kuluttavien ryhmissä. Toisaalta nollakäyttäjienkään kuolleisuus ei ollut kohtuukäyttäjiä suurempi viitaten siihen, että pitkällä aikavälillä alkoholin kohtuukäytöstä ei välttämättä ole terveydellistä hyötyä abstinenssiin verrattuna.

Kun laskennassa otettiin huomioon se, että suurimpaan alkoholinkuluttajaryhmään liittyi myös runsaammin muita riskitekijöitä (mm. tupakointi, vähäinen liikunta, korkeampi verenpaine) ja näiden tekijöiden vaikutus eliminoitiin kuolleisuutta laskettaessa, ei alkoholin käyttö enää yksinään sinänsä lisännyt kuolleisuutta. Alkoholia enemmän kuluttaneiden suurempi kuolleisuus näyttää siis liittyvän enemmänkin alkoholin käyttöön liittyviin muihin riskitekijöihin kuin alkoholin itsenäiseen vaikutukseen tässä mieskohortissa, joka oli keski-iässä terve ja työkykyinen. On lisäksi huomioitava, että alkoholin ongelmakäyttö oli poissulkukriteeri tässä tutkimuksessa.

2.5 OSATUTKIMUS IV: KESKI-IÄSSÄ TAPAHTUNEEN TUPAKOINNIN YHTEYS KUOLLEISUUTEEN JA VANHEMMAN IÄN ELÄMÄNLAATUUN.

Neljännen osatutkimuksen tulokset keski-iässä tapahtuneen tupakoinnin yhteydestä kuolleisuuteen ja vanhemman iän elämänlaatuun osoittivat, että keski-iässä tupakoimattomat miehet elivät 10 vuotta pitempään kuin yli 20 savuketta päivässä polttaneet. Tämä siitä huolimatta, että lähes 70 % tupakoitsijoista oli lopettanut tupakoinnin seuranta-ajan kuluessa. Tupakoimattomien miesten elämänlaatu oli 26 vuoden seurannassa paras kaikilla RAND-36 mittarin asteikoilla mitattuna. Erityisen suuret erot keski-iässä tupakoineisiin nähden nähtiin fyysisessä toimintakyvyssä ja fyysisten ongelmien aiheuttamissa roolitoiminnan rajoitteissa. Eloonjääneiden tupakoitsijoiden fyysinen toimintakyky oli tasolla, joka keskimäärin vastasi 10 vuotta vanhemman suomalaisen miesväestön toimintakykyä RAND-36 mittarin Fyysinen toimintakyky -asteikolla mitattuna.

2.6 OSATUTKIMUS V JA VI: VERISUONISAIRAUKSIEN RISKITEKIJÖIDEN KASAUTUMINEN KESKI-IÄSSÄ, KUOLLEISUUS JA ELÄMÄNLAATU VANHALLA IÄLLÄ.

Osatutkimuksessa V ja VI verrattiin keski-iässä korkean ja matalan valtimosairauksien riskitekijätason omaavien, mutta muuten terveiden miesten kuolleisuutta ja elämänlaatua 26 vuoden seurannan aikana. Sydän- ja verisuonisairauksien riskitekijöiden kasautuminen aiheutti yli 50 % suuremman suhteellisen kuolleisuuden seuranta-aikana. Eloonjääneistä miehistä niillä, joiden valtimosuonisairauksien riskitekijätaso keski-iässä oli matalampi, oli seurannassa kauttaaltaan myös parempi elämänlaatu kuin niillä, joilla oli yksi tai useampia riskitekijöitä: RAND-36 mittarin kaikki kahdeksan asteikkoa osoittivat parempaa elämänlaatua. Kokoomamuuttujista myös fyysistä terveydentilaa kuvaava PCS oli parempi, mutta psyykkistä terveydentilaa kuvaava kokoomamuuttuja MCS ei merkitsevästi eronnut ryhmien välillä.

Kuitenkin, kun osatutkimuksessa VI selvitettiin näiden ryhmien henkistä hyvinvointia erillisellä kartoituksella vielä laajemmin, kuin mitä RAND-36 kysymyssarja mahdollistaa, todettiin eroja myös psyykkisen elämänlaadun osalta. Kyselykaavakkeilla selvitettiin masennusoireita, onnellisuuden tunnetta ja positiivista elämänasennetta. Tulokset olivat järjestelmällisesti parempia matalan riskiryhmän hyväksi. Merkitsevät erot nähtiin elämään tyytyväisyydessä, onnellisuudessa, positiivisessa elämänasenteessa, Zungin depressiopisteissä sekä yleisessä terveydentilassa.

Tulokset kuvastavat sitä, että keski-ikäisenä matalan riskitason omaavat miehet vanhenivat myös psyykkisesti terveempinä kuin korkean riskin miehet.

2.7 YHTEENVETO

Elintapoihin, kuten ruokailutottumuksiin, tupakointiin tai alkoholinkäyttöön liittyvät valinnat vaikuttavat oleellisesti elämämme pituuteen. Pitempi elämä ei kuitenkaan takaa parempaa terveyttä tai parempaa elämänlaatua, etenkään elinkaaren lopussa. Pitkäikäisille jää enemmän aikaa sairastua valtimotauteihin tai muihin kroonisiin sairauksiin, jotka saattavat alentaa toimintakykyä ja elämänlaatua. Väestön ikääntyessä ihmisten viimeisten vuosien itsenäinen toimintakyky, sekä henkinen ja sosiaalinen hyvinvointi ovat keskeisiä sekä yksilön että yhteiskunnan kannalta. Tämän vuoksi elämänlaadun arvioinnista on tullut tärkeä mittauskohde kuolleisuuden ja sairastavuuden rinnalle.

Tässä väitöskirjassa esitettyjen tutkimustulosten mukaan valtimosairauksien matala riskitekijätaso keski-iässä ja myöhemminkin lisää merkittävästi vanhuusiän elämänlaatua, erityisesti fyysistä toimintakykyä, mutta usein myös psyykkistä

hyvinvointia. Terveelliset elintavat siis paitsi lisäävät elinvuosia, myös parantavat niiden laatua. Täyden hyödyn saamiseksi riskitekijöiden tunnistamisen ja hoidon tulisi tapahtua riittävän varhaisessa vaiheessa, keski-iässä tai nuoruudessa. Tieto tulevan vanhuusiän elämänlaadun parantumisesta voi myös osaltaan lisätä yksilön motivaatiota elintapamuutoksiin.

3 CONTENTS

4 LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original articles, referred to in the text by Roman numerals. In addition, some previously unpublished data are presented.

I

Strandberg TE, Strandberg A, Salomaa VV, Pitkala K, Miettinen TA. Impact of midlife weight change on mortal ty and quality of life in old age. Prospective cohort study. Int J Obes Relat Metab Disord. 2003; 27:950-4.

II

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III

Strandberg AY, Strandberg TE, Salomaa VV, Pitkala K, Miettinen TA. Alcohol consumption, 29-y total mortality, and quality of life in men in old age. Am J Clin Nutr. 2004; 80:1366-71.

IV

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V

Strandberg A, Strandberg TE, Salomaa VV, Pitkala K, Happola O, Miettinen TA. A follow-up study found that cardiovascular risk in middle age predicted mortality and quality of life in old age. J Clin Epidemiol. 2004; 57:415-21.

VI

Strandberg TE, Strandberg AY, Pitkala K, Salomaa VV, Tilvis RS, Miettinen TA. Cardiovascular risk in midlife and psychological well-being among older men. Arch Intern Med. 2006; 166:2266-71

5 LIST OF ABBREVIATIONS

ADL= activities related to daily living
ASA = acetosalicylic acid
ACE = angiotensin-converting-enzyme
ANCOVA= analysis of covariance
BMI = body mass index
BP= blood pressure
CHA= Chicago Heart Association Detection Project in Industry
CHD = coronary heart disease
CI = confidence interval
COM = compression of morbidity
CUA = cost-utility analysis
CV = cardiovascular
CVD = cardiovascular disease
DALY= disability-adjusted life year
ECG = electrocardiography
ELSA = English Longitudinal Study of Aging
gamma GT = gamma-glutamyl transpeptidase
GDP = gross domestic product
HDL = high-density lipoprotein
HRQoL = health-related quality of life
LDL= low-density lipoprotein
MCS = mental component summary
MOS = Medical Outcomes Study
NCSS= number crunching statistical system
NHANES = The National Health and Nutrition Examination Survey
OR = odds ratio
PCS = physical component summary
PF = Physical functioning
QALY = quality-adjusted life year
QoL = quality of life
RAND-36 = RAND 36-Item Health Survey (Version 1.0)
RH = relative hazard
SD = standard deviation
SEM = standard error of measurement
SF-36 = MOS 36-Item Short Form Health Survey
SES= socio economic status
SBP = systolic blood pressure
T2D = type 2 diabetes, adult-onset diabetes
TIA= transient ischaemic attack
VAS = visual analogue scale
WHO = World Health Organization
WW2 = World War II

6 INTRODUCTION

Life can only be understood backwards; but it must be lived forwards.
(Søren Kierkegaard, Danish philosopher (1813 - 1855))

The world's population is aging.[1] Globally this is due to reduced fertility and increased life expectancy. In the developed societies this is mainly because of the great birth rate after the two decades following WW2, while advances in public health through behavioral changes, nutrition and improved medical care have diminished mortality.

Consequently, there will be more people who can expect to live a full lifespan and an increased number of persons over 65 years of age during the years 2010-2030.[2] In Finland 80% of men and 90 % of women are expected to live to the age of 65 years or older. The age of 80 is reached by nearly one-half of men and 70 per cent of women.[3] The increase in life-expectancy is largely attributed to a decline in cardiovascular mortality via a reduction in major risk factors as well as advances in the treatment of these diseases.

As people reach older ages, also the morbidity of chronic diseases and subsequent disability and functional impairment among the population is anticipated to increase. This has highlighted the importance of improving the quality of life and functional abilities of older adults, both from the individual as well as the societal point of view. Subsequently, an individual's own view on his or her well-being has become an increasingly significant measure of health along the traditional measures such as mortality and morbidity. The development of validated questionnaires, for example RAND-36, has made it possible to collect information on this subjective health outcome for the purposes of clinical practice and research as well as determining health policies.

7 REVIEW OF THE LITERATURE

7.1 HEALTH-RELATED QUALITY OF LIFE

7.1.1 DEFINITION OF QUALITY OF LIFE

Quality of life (QoL) remains still poorly defined today. It is a multidimensional concept that refers to the overall well-being of individuals.[4] In the broadest sense it includes major economical, social and environmental components besides health, such as literacy, income and freedom. This general view is represented in the United Nations Development Program's Human Development Index, HDI[5], which is the best known composite quality of life scale.[6] This index was developed in order to make comparisons between different countries. It gives a single value measuring health and longevity, knowledge (literacy and school enrolment) and standards of living (GDP per capita). Numerous other indices have been developed to measure quality of life. As basic markers they typically include factors such as income, employment, poverty, health status, family issues and pollution levels.[6]

However, many of the non-economic aspects of the quality of life are subjective and cannot be objectively measured. Thus several indices, for instance the WHOQOL [7] [8] questionnaires have been constructed to encompass not only the quality of life circumstances, but also dimensions that cover an individual's perceptions and feelings to his living conditions in the context of his environment, culture, values, and experiences, including measures of satisfaction or happiness.[9] [10] Spilker et al. have divided the concept of quality in life in gerontological research into two distinct concepts: the health-related quality of life (HRQoL) and the non-health environmental-based quality of life. [11]

7.1.2 DEFINITION OF HEALTH-RELATED QUALITY OF LIFE

The World Health Organization (WHO) has in 1948 defined health as being not only the absence of disease but also the presence of physical, mental, and social well-being: *"A state of complete physical, mental and social well-being and not merely the absence of disease or infirmity."*[12] This definition of health thus considers also aspects related to the quality of life (QoL). Subsequently, the concept was expanded

to also include health-related quality of life (HRQoL), when in 1993 WHO presented a definition of quality of life linked to health: *"An individual's perception of his/her position in life, in the context of the culture and value systems in which he/she lives and in relation to his/her goals, expectations, standards and concerns"*. [7]

It meant a decisive shift from measuring only ill health and its manifestations with traditional measures such as morbidity and mortality, to measuring health status multidimensionally with additional measures such as physical functioning, cognitive and emotional functions and self-perceived health.

There is a variety of other definitions also for the HRQoL, but they all have in common that the emphasis is upon the perspective of the individual. For example, the Encyclopaedia of Aging defines that *"HRQoL refers to how health impacts on an individual's ability to function and his perceived well-being in physical, mental and social domains of life"*.[13]

7.1.3 MEASURING HEALTH-RELATED QUALITY OF LIFE

HRQoL may be measured for various purposes, principally in order to 1) differentiate the health status between groups, 2) evaluate change over a period of time or 3) predict future health states.[14] Subsequently different prerequisites are needed for the profile of the HRQoL instrument in question, according to the rationale. Ideally a HRQoL instrument should be able to perform two important properties: To measure important health domains widely, and to have the ability to integrate the data from the individual domains into an overall score.[15] An overall score is required for cost-utility evaluations. Typically HRQoL domains include an assessment of functional status (e.g. how long a person is able to walk or run, whether he is able to do housework or bathe or dress independently), emotional well-being or mental health (e.g. signs of depression or anxiety or positive affect), social involvement (e.g. engagement in activities) and symptom states (e.g. pain, sleep). A common feature of HRQoL domains is that they include characteristics of life which are affected by changes in health. Jaschke et al. have defined that HRQoL domains are aspects of life that improve when a physician successfully treats a patient.[16]

7.1.3.1 Types of measure

According to Fitzpatrick [17] and Garratt et al. [18] HRQoL questionnaires are divided into different types of measure:

1) Dimension specific measures usually produce a single score focusing on a specific aspect of health, for instance the Zung Self-Rating Depression Scale.[19]

2) Disease or population targeted measures are aimed to be used in specified diseases such as asthma or arthritis, for instance the Asthma Quality of Life questionnaire.
3) Generic measures are designed to be responded to by anyone so that they are applicable across all diseases and conditions, across different medical interventions and across a wide range of populations and they usually include a number of health domains. Generic measures have the advantage to compare the health state of different groups, for instance the young and the old or the ill and the healthy, and to make comparisons of the burden of disease in different conditions and to compare the benefits of different treatments. For instance The RAND 36-Item Health Survey. [20]
4) Individualized measures permit respondents to assess and value aspects of their own life*;* usually to generate a single score, for instance the patient generated index.[21]
5) Utility measures have been developed for purposes of economic evaluation. They focus on preferences for health states. They produce a single index for use in economic evaluation. For instance EuroQoL [22] and Health Utilities Index [23].

Another categorization of HRQoL measures divides them into disease-specific and generic measures, as suggested by Patrick [24] and Fayers [25].
1) Disease-targeted HRQoL measures are aimed to be used in specified diseases such as depression or arthritis.
2) Generic measures, as described above, can be used to assess the health of both general and specific populations. Generic measures are further divided into two types of generic HRQoL measures:
   a) Profile measures, such as RAND-36, which give scores on multiple aspects of HRQoL.
   b) Contrary to this, preference-based generic HRQoL measures produce a single summary score for HRQoL, which is needed especially when an economic value of the change or differences of treatment is to be evaluated.

7.1.3.2 Reliability and validity

The HRQoL instrument used in research or a clinical study has to be reliable and valid. Psychometric methods are used to establish the quality of the HRQoL instrument and the measurements.

7.1.3.2.1 Reliability

In the context of a HRQoL instrument with multi-item scales, reliability is usually measured by examining its internal consistency and test-retest reliability. Higher reliability indicates that random error has less part in the results.

The internal consistency reliability of a HRQoL survey instrument reflects how well different questionnaire items are interrelated and thus indicates whether their combination in an index is justified. The most common method to test this is Cronbach's alpha (α). [26] It ranges from zero to one; commonly for group comparisons an α of 0.7-0.8 is regarded to indicate acceptable reliability and 0.8 or higher indicates good reliability. [27] In a multi-item questionnaire Cronbach's alpha depends on the number and the homogeneity of the items. Reliability can thus be increased by increasing the number of items in the questionnaire. [28] However, this may have a negative effect on the feasibility of the questionnaire.

The test-retest method is needed to evaluate reliability, if the questionnaire is administered several times. A reliable HRQoL instrument should be able to give the same score for the same person or group each time it is administered, when there has been no change in the attribute that is measured.

7.1.3.2.1 Validity

It is important that a HRQoL scale is valid for the specific application in the determined population. Validity refers to whether the HRQoL instrument measures what it is expected to measure.

In general there are three kinds of validity used for the evaluation of a HRQoL survey instrument: Content validity, construct validity and criterion-related validity. [29]

Content validity means the ability of the HRQoL instrument to cover all the aspects of health dimensions that were intended to be evaluated.

Construct validity reflects to the ability of a test to measure the concept that it is supposed to measure. It is often evaluated by examining the relationship of the item to be validated to other related items in the survey.

Criterion-related validity is examined by comparing the results of the test instrument to the results given by another instrument regarded as the golden standard for this purpose.

Floor and ceiling effects are concepts that may affect the criterion validity of a HRQoL instrument. Floor effect takes place when the HRQoL instrument cannot differentiate those respondents whose scores are at the bottom of the scale. Ceiling effect is the opposite phenomenon at the top of the scale. For instance, asking a group of joggers whether they can walk 2 kilometers does not distinguish possible differences in their fitness, producing a ceiling effect. Respectively, if the question is posed to people in wheelchairs, a floor effect is apparent.

The instrument measuring HRQoL should also detect change in a clinical intervention. In a cross-sectional study an ability to distinguish among groups in a point in time is required. The capability to detect within-person change over time and ability to predict subsequent health status are needed in a longitudinal study.[30]

In addition, the concept of responsiveness, defined as the capability of an instrument to detect clinically relevant change over time, has been added to the basic qualifications of an evaluative HRQoL tool. [31] However, its definition varies [32] and furthermore, it has been repeatedly debated whether this is a distinct asset of HRQoL questionnaires separate from reliability and validity, or simply a measure of longitudinal validity or of treatment effect. [33]

7.1.3.3 Person reported information

A central feature of practically all HRQoL measures is that individuals themselves rate their level of disability or well-being. Questionnaires assessing the HRQoL of the respondents are an easy and inexpensive way to collect information about the health of the participants and the course and changes of their health over time. As a result, self-administered questionnaires have nowadays been widely accepted for use in clinical studies of large population samples as they enable gathering data from a large cohort simultaneously at a lot less expense than clinical assessments. Furthermore, the relative privacy of the respondent may diminish bias resulting from incomplete or false answers to questions that the participant finds inappropriate or too personal in interviews.

Single global assessments with a one-item questionnaire of self-perceived health or HRQoL have been used when a single score for a patient is needed for instance for health economics or policy making. However, most HRQoL instruments are multi-item questionnaires, covering the many aspects of HRQoL.

7.1.3.4 RAND-36

The RAND 36-Item Health Survey (Version 1.0) / The MOS 36-Item Short Form Health Survey (SF-36®) was developed in 1988-1990 from the data gathered from a cohort of over 20.000 patients participating in the Medical Outcomes Study (MOS). [20] [34] MOS was a multi-year, non-experimental study of patient outcomes conducted in the U.S. during the 1980's. [35] The HRQoL measures in the MOS study were gathered by self-administered questionnaires consisting of 116 items covering the two dimensions of health: physical and mental health. With further analysis and development, these questions were later cut down to a subset of 36 items reflecting functioning and well-being. This 36-item set is currently distributed by

different organizations, with subsequently different names. The RAND organization is distributing the set as the RAND 36-Item Health Survey 1.0 (RAND-36), the Medical Outcomes Trust as the MOS 36-Item Short Form Health Survey (SF-36) [36] , the Health Outcomes Institute as the Health Status Questionnaire and the Psychological Corporation as the RAND-36 Health Status Inventory.

By 1991, RAND-36 had been shown to be a reliable, valid and responsive instrument in measuring HRQoL by several clinical studies in the U.S. [18] [37] Research had shown it to be a comprehensive measure of generic health status that was applicable across heterogeneous populations, including older people. [38] [39] Due to its shortness it could be supplemented with other generic and disease-specific measures in clinical studies. During the 1990's, studies in several European countries showed that it could be translated successfully. The Finnish version of RAND-36 was jointly developed by RAND, Stakes and Kansanterveyslaitos in 1994. [40] It has been validated as a mailed questionnaire also for the Finnish general population with age- and sex-matched population norms.

According to a systematic search of electronic databases in 2002, RAND-36/ SF-36 is the most widely used generic health outcomes instrument in the world. [41] It accounted for over 10% of the total number of reports, including those using disease-specific measures, and more than 60% of those using a generic measure. Translations are available for more than 60 countries and more than 5.000 papers have been published using RAND-36/SF-36 to measure HRQoL. [42] Despite similar wording in the questions, the scoring algorithm for the scales of bodily pain and general health somewhat differ between RAND-36 and SF-36. However, these differences have been shown to be of minor importance and do not have a meaningful effect on the scale scores. [34] A practical difference in using these questionnaires is that the MOS Trust Corporation demands permission for use and strict adherence to item wording and scoring recommendations in order to allow the use of the SF-36 trademark, whereas the RAND-36 questionnaire is freely distributed without copyright protection.

7.1.3.4.1 Construction of RAND-36

The RAND-36 /SF-36 questionnaire is comprised of 36 items (questions) that assess eight domains of HRQoL:

1) Physical functioning:
   Includes ten items, describing to what extent the respondent's health limits his or her physical activities such as walking distance, ability to climb stairs, lifting objects, bending or kneeling.

2) Role limitations caused by physical health problems:
   Includes four items describing limitations in activities caused by physical problems,
3) Role limitations caused by emotional problems:
   Three items, describing limitations in activities that are due to emotional problems,
4) Social functioning:
   Two items covering the extent of limitations in normal social activities caused both by physical or mental factors,
5) Emotional well-being:
   Five items covering happiness, anxiety and depression,
6) Energy/fatigue:
   Four items reflecting the respondent's vitality and tiredness,
7) Pain:
   Two items on the magnitude of pain and the amount it interferes with daily activities,
8) General health perception:
   Five items on self-perceived conception on one's current health, current health state compared to others, future health and resistance to illness.

The 36 th item (question number 2) in the RAND-36 questionnaire is a single item that assesses the change in perceived health during the past 12 months. It is not counted into the scales or summary scores.

Responses to these 36 questions vary from dichotomous (two answers e.g. yes or no) up to six alternatives in answers (e.g. none/some of the time/most of the time etc.), with five or six options being the most common response categories.

All items are transformed linearly such that the lowest and highest scores are set at 0 and 100, respectively. Thus all scales scores range from 0 to 100, with 100 representing the most favorable functioning or well-being, and the scale scores characterize the percentage of total possible score that can be attained.

7.1.3.4.2 RAND-36 component summary scores

The eight domains of RAND-36 are further aggregated into two summary measures: the physical (PCS) and mental (MCS) health component summary scores. These summary scales are standardized so that the mean (+/- SD) for the validated population is 50 (+/- 10). Subsequently, for example a score under 50 is thus below the general population mean, and each point corresponds to 1/10th of a standard deviation. The summary measures have not been validated in the Finnish population.

7.1.3.4.3 Reliability and validity of RAND-36

Since RAND-36 can be utilized in various different populations, in different languages and for diverse applications, evidence of its reliability and validity is essential for its use.

The validity of the RAND-36 scales has been analyzed as part of the MOS study core measures by means of content, construct, and criterion validity. [20] Also data from clinical studies and population surveys have been assessed for this purpose. [37] The scales have also been evaluated for reliability coefficients such as inter-rater reliability, internal consistency reliability and test-retest reliability. Estimated with Cronbach's alpha coefficient the RAND-36 scales were shown to be reliable both for group and individual cmparisons. [43]

While the multi-item structure of generic measures such as RAND-36 conveys many benefits, small changes in responses may be hidden behind the stability of the other items and thus reduce the responsiveness of the instrument. [44]

7.1.3.4.4 Minimal clinically important difference

A small difference in a HRQoL score may in a clinical study be statistically, yet not necessarily clinically significant. The concept of minimal clinically important difference (MCID) has been created to denote the smallest difference in an outcome measure e.g. a HRQoL score that would still be clinically important. For instance, in a clinical study, a change in a HRQoL domain that gives reason for a change in treatment can be regarded as a clinically significant change. [16]

Although MCID standards have not been clearly established for the RAND-36, a difference of 3 to 5 points has been suggested. [45] [46] Changes in scores that exceed one standard error of measurement (SEM) have also been regarded as a significant clinical change for RAND-36. [47] *(SEM is calculated as SD √(1 – R) where SD is the SD of the baseline domain score and R is the domain reliability.)* In a meta-analysis of 38 studies using different HRQoL instruments, Norman et al. found that MCID was consistently very close to one half a SD in these studies. [48]

7.1.3.4.5 The predictive value of RAND-36

Self-assessed health status has been shown to be a strong predictor of subsequent mortality and morbidity [49] [50], and this has also been demonstrated for the RAND-36/SF-36 questionnaire [45], also among older persons [51].

The RAND-36/SF-36 questionnaire was developed from the data gathered in the Medical Outcomes study. In this study the 5-year mortality rates of chronically

ill participants increased markedly with the decline in PCS scores. [45] The mortality was 21.5% for those whose PCS score was 8- 24; 15.1% for PCS score 25-34; 6.2% for PCS score 35-44; 4.7% for PCS score 45-54, and 1.8% for PCS score 55-72.

Kroenke et al. examined the predictive value of the SF-36 instrument for mortality among healthy middle aged women in a large sample of the Nurses' Health study population, showing that women with low PCS and MCS scores had the highest mortality during the 4-year follow-up. [52] A great decline in PCS was associated with over a three-fold relative risk compared to those women with no change in PCS. Improvement in PCS was associated with lower mortality. Results for the MCS score were similar. In a study of 2.166 older participants with chronic diseases, the PCS of SF-12, the shortened version of SF-36, predicted higher mortality and hospitalization during two years of follow-up.[53] In another prospective study of 7.702 participants a decline of more than 10 points in the PCS score was associated with over two-fold increased risk for mortality and 1.8 fold risk for hospitalization during a year of follow-up. [54] An increased risk was also seen with a more than 10-point decrease i the MCS: 1.6 fold risk for morality and 1.5 fold risk for hospitalization. Also in the healthy and relatively young cohort of the Whitehall II study, SF-36 was shown to be able to detect changes in the health status in the general population. [55]

Additionally, the Physical functioning scale has been shown to be independently comparable to other instruments measuring disability in older people. [56] While in some studies the patients' own assessments of their physical functioning seems to differ from the evaluation made by a physician,[57] a systematic review of trials showed that on average the doctors' global assessments of treatment effects are comparable to those of patients. *[58]*

7.1.3.4.6 Floor and ceiling effect

Using SF-36 in the general population, floor effects have been observed in the two Role limitations scales in the general U.S. population.[59] The ceiling effect has been observed for the two Role limitations scales as well as for Social functioning. In a study of healthy older participants, some tendency for ceiling measurement effects was seen in two physical scales of SF-36. [60] Whether these effects are imposed in very ill patients has not been determined.[61] In the Finnish general population floor effects were found in the Role limitation scales and stronger ceiling effects were apparent in the scales of Role limitations, Physical functioning, Social functioning and Bodily pain of the RAND-36 instrument. These effects were stronger than those found in the U.S. general population.[40]

7.1.3.4.7 Missing data

A possible limitation of self-administered questionnaires especially in studies involving older persons is missing data.[62] Although they are easier and cheaper to perform than personal interviews, the amount of missing data is greater in mailed questionnaires. Missing responses may lead to bias by diminishing the power of analysis or enhancing variation in parameter estimates. The amount of missing data may increase according to the age of respondents. In the MOS study older patients were more likely to miss an item within a given HRQoL measure; 12 % of respondents 75 years or older had missing data for at least one of the 10 items of the PF scale.[63] However, very few patients in any age-group missed all items in a measure. Higher education diminished the rate of missing data. In this study, 10% of participants over 75 years and with poor physical or mental health felt unable to self-complete the SF-36 questionnaire and 26% of them left out at least one of the 36 items. Also missing statements were significantly related to older age. Parker et al. found that overall functional impairment, cognitive impairment and impaired manual dexterity were associated with the number of uncompleted items, whereas cognitive impairment, age and visuospatial problems increased the time to complete the SF-36 questionnaire.[64]

On the other hand, in a multi-item questionnaire, such as RAND-36/SF-36, the missing data may be imputed by an estimation of the respondent's answers to the other items in the scale. This increases the reliability of the RAND-36 HRQoL instrument compared to a measure using only one or two items.

In end-of-life studies, such as the Helsinki Businessmen Study, also death leads to missing data. When two groups are compared, the group with higher mortality and missing data will be likely to have the most favorable data, if deaths are not accounted for. Diehr et al. have developed a coding for self-perceived health that encompasses death as an outcome, offering an approach to combine self-assessed scores with mortality data. [65] [66] These analyzes produce new alternate values for PCS and MCS where the dead areo coded as zero.

7.2 SUCCESSFUL AGING

7.2.1 DEFINITION

In 1998 WHO introduced the concept of active aging: *"Active aging is the process of optimizing opportunities for health, participation and security in order to enhance quality of life as people age."* [67] This concept is applicable both at the individual as well as at the population level. Besides health, it takes into account aspects of social

and environmental factors needed for active life in old age. This is an important paradigm, because older people estimate their quality of life differently from the general population, weighing besides health such parameters as social relationships and comparisons, dependency and material circumstances.[68]

Another related concept, successful aging, was introduced in the 1950's, characterizing the factors and conditions fundamental for healthy aging.[69] In 1987 Rowe and Kahn [70] examined the concept of successful aging, stating that the modifiable factors affecting the aging process, e.g. diet and exercise among other things, have been underestimated. A large proportion of the features of the aging process is attributed to lifestyle and other issues that are not due to aging itself, although they may increase with age. Analogous to the WHO definition of quality of life, they have later defined successful aging as not just the absence of disease in old age, but it covers the mental and social aspects as well. They concluded that successful aging includes three major components: *"low probability of disease or disease-related disability, high cognitive and physical functional capacity and active engagement with life"*. [71] In this definition, *the probability of disease* encompasses the cardiovascular risk factors present earlier in life, affecting the later functional capacity, which again is needed in order to successfully attend different activities in old age. In this sense, successful aging is highly equivalent with good HRQoL in old age.

However, there are various other definitions for successful aging. In a review of larger studies, Depp et al.[72] found 29 definitions in 28 studies. Most of these definitions were based on the absence of disability, omitting mental or social variables.

7.2.2 COHORT STUDIES ON SUCCESSFUL AGING

Depp et al. also concluded that among the total of over 500 studies investigating successful aging, less than 20 have been prospective studies, thus most studies are restricted to survivors. This reflects the fact that although the effect of midlife risk factors on mortality is well known, long term studies with large numbers of long-lived subjects and baseline lifestyle information on healthy aging are scarce. One of them is the Honolulu Heart Program/ Honolulu Asia Aging Study (HHP/HAAS), which has followed a cohort of 5.820 Japanese American men for 40 years.[73] In this study a higher number of common modifiable risk factors, such as overweight, smoking, excessive alcohol consumption, low physical activity, hyperglycemia and hypertension at the age of 55 years were inversely related to successful aging. The men with no risk factors in midlife had a probability of 72% to be alive and healthy at the age of 75 years, whereas those with 6 or more risk factors had a probability

of 43% to attain this age free of defined morbidities or physical or cognitive disability. The probabilities to achieve the age of 85 years healthy were 55 % and 9%, respectively. Education level was associated with successful aging, whereas marital status generally did not have an impact on healthy aging in this cohort.

Similarly, even at the age of 72 years, when selection has already occurred, the absence of the five traditional modifiable risk factors (smoking, obesity, diabetes, hypertension and sedentary lifestyle) increased longevity and decreased morbidity and disability in a prospective study of healthy male physicians.[74]

The data from the Cardiovascular Health Study (CHS) highlighted the significance of subclinical vascular disease in successful aging. [75] However, the many reports from one of the world's longest follow-up studies on aging, the Baltimore Longitudinal Study of Aging (BLSA) suggest a much more complicated background: with old age, there may be a dysfunction in the homeostasis of the body, making it more vulnerable to risk factors and subsequent disease.[76]

Genetic factors have been shown to influence the human life span by 15-30% and this impact may accelerate after the age of 60 years.[77] [78]

Yet, while these novel findings will have implications for preventive measures in the future, the importance of the prevention of the traditional modifiable cardiovascular risk factors remains paramount.

7.3 COMPRESSION OF MORBIDITY

A direct extension to the concept of successful aging is the hypothesis of the Compression of Morbidity (COM), which was first presented by Fries in 1980, [79] postulating that with preventive measures of chronic illness in the aging society, the postponement of death would also lead to a delay in the onset of disability. The prerequisite is that the gained postponement in the onset of disability is greater than the delay in death, leading to a net reduction in the lifetime burden of illness.

Accordingly, this compression is expected to be greatest in preventing health states that do not change life-expectancy, but have an effect on disability, for instance osteoarthritis or Alzheimer's disease, in contrast to the prevention of cardiovascular diseases or cancer, which also may lead to a decline in the mortality rates. The latter scenario produces a later onset of disability, but may also increase the number of years lived with disability, and subsequently increase the cumulative lifetime burden of disease and in fact lead to an expansion of morbidity in this case. Therefore, in order to a true compression of morbidity to happen, the prevention should lead to a greater postponement of the onset of disability than the postponement of death. Whether the prevention of major cardiovascular risk factors can lead to COM has not been established. Cardiovascular risk factors effect health early on in life, as in

the case of smoking for instance. To evaluate the impact on COM, a longitudinal study covering the whole lifespan is needed.

Data in the U.S. shows, that while longevity has been increasing at about 1 % per year, the disability rates of older adults have been declining steadily about 2% per year,[80] indicating that at the population level morbidity and disability are being compressed towards the end of life. However, the scope may not be wide enough, neither from the individual's point of view nor from the society's benefit, if only disability is taken into account. Instead, the quality of these final years includes more than just disability, which is often equal to physical fitness. In order to fully quantify the benefit, the quality of these years should be measured with a valid instrument taking also the mental and social aspects of life into account. Besides the fact that living longer in good health is significant for the individual, the evaluation of COM is of crucial significance for the aging society, where the increasing costs of health care demand estimates also of the financial burden of disease.

7.4 CARDIOVASCULAR RISK FACTORS AND MORTALITY

7.4.1 TRENDS IN CARDIOVASCULAR MORTALITY

Mortality due to cardiovascular diseases (CVD) and especially to coronary heart disease (CHD) in Finland and other developed countries underwent substantial changes during the 20th century. Gradually increasing to the late 1960's, age-adjusted death rates due to CVD were halved from 1970 to 2000 [81] and the declining trend is still continuing.[82]

Despite this favorable trend, still in 2004, CVD are the leading cause of death in the developed countries.[83] According to WHO one of every third death is caused by CVD, about 17 million people a year globally. Heart disease and stroke are estimated to become the leading cause of both death and disability worldwide by the year 2020 with over 20 million deaths each year. [84] Almost half of all deaths in Europe are caused by CVD. In Finland, more than a third of total mortality was due to CHD or stroke among both men and women over 65 years in 2007. [85] Among men aged 15-64 years, CHD was the second most common cause of death, accounting for 16% of total mortality in this age group. These figures are higher than in most countries in Western Europe. While the age-adjusted cardiovascular mortality has declined, the total number of those with CVD has increased among older people, indicating that the morbidity has shifted to older age groups, especially among women.[82]

7.4.2 THE CONTRIBUTION OF RISK FACTOR DECLINE TO CHD MORTALITY

The decline in mortality has in part been accomplished by major advances in modern medication and technology such as thrombolysis, coronary-artery bypass grafting (CABG), coronary angioplasty and stents, as well as amplified secondary prevention with the use of medication such as ASA, statins and ACE-inhibitors. But even greater an impact has been achieved by primary prevention of these diseases by means of changed lifestyle, diet and medication.

Several causal risk factors of CVD have been identified. Among them, high blood pressure, smoking, elevated cholesterol and type 2 diabetes (T2D) were individually the first four most important factors attributed to death in countries of high income in 2001.[86] Together with alcohol they were also the main causes for the disease burden as measured by disability-adjusted life years (DALYs).[87] In Finland in 2007, alcohol-related diseases or accidental alcohol poisoning were the leading cause of death for both men and women in the age-group of 15 to 64 years.[85]

The importance of reducing these risk factors has been shown in several population studies presenting declining rates of cardiovascular morbidity and mortality with the modification of risk factors. [88] [89] [90] In Finland, Vartiainen et al. [91] observed a 55% and 68% decline in coronary heart disease mortality in men and women, respectively, from 1972 to 1992. This was principally due to favorable changes in the three major risk factors, serum cholesterol, smoking and blood pressure during this period. Similarly, Laatikainen et al. [92] estimated that more than half of the decline in deaths from CHD from 1982 through 1997 in Finland may be attributable to reductions in major population risk factors for CHD (smoking, high blood pressure and elevated total cholesterol). Using U.S. data, Ford et al. [93] determined that approximately 50 % of the decline in U.S. deaths from CHD from 1980 through 2000 may be ascribed to the positive changes in major risk factors and about 50 % to medical and surgical treatments for CHD, including hypertensive medication and primary prevention with statins. The prospective British Regional Heart Study showed a 46% reduction in the incidence of myocardial infarction due to favorable changes in CV risk factors over the follow-up period of 25 years. The decline in cigarette smoking was attributed to half of this reduction.[94]

However, lately the prevalence of both obesity and T2D has increased and it is now commonly feared that this unfavorable trend may offset the benefits gained from the decline of other risk factors. [95] [96] Besides, cardiovascular risk factors are often clustered. Cardio-metabolic risk factors such as overweight or obesity, hyperlipidaemia, T2D, and hypertension are prone to be present in the same individual and result in an elevated risk of CVD and mortality. E.g. 80 % of hypertensive patients have other risk factors as well, and the majority of them are overweight. [97] Higher BMI is also associated with elevated lipid levels.[98] Weight gain and obesity are primary causes for hyperglycemia and T2D and the metabolic

syndrome.[99] Furthermore, the metabolic syndrome is a multiplex risk factor for both CVD and T2D.[100] Also most of the patients with established CVD have multiple risk factors.

7.5 CARDIOVASCULAR RISK FACTORS AND COSTS

On the societal level, the direct and indirect costs for CVD are still a major part of health care costs in the developed countries and they have continued to rise. In allocating resources in a purposeful way, an evaluation of the cost effectiveness of prevention of cardiovascular disease is needed. In Finland, the direct health care costs induced by obesity, low physical activity, smoking and alcohol were estimated at about one billion Euros.[101] Costs associated with subsequent diseases are partly overlapping, but the direct cost of diabetes alone was estimated at 500 million Euros. However, while a body of evidence shows the benefits of cardiovascular risk factor reduction on subsequent disease, the cost effectiveness of health promotion among the general population in this field has not been studied extensively.[101] Direct costs on health care are only a part of the economic burden and it is more difficult to evaluate the indirect costs due for instance to work absenteeism or different aspects of long term geriatric care induced by cardiovascular risk factors and subsequent disease. Using Medicare data in the U.S., Daviglus et al. showed that fewer midlife cardiovascular risk factors predicted lower heath care costs towards the end of life.[102] Indirect costs associated with cardiovascular risk factors are already seen during active work age: Sullivan et al. showed that common cardiovascular risk factors have a harmful effect on work ability: individuals with concurrent cardio-metabolic risk factors missed 179% more work days and spent 147% more days in bed (in addition to lost work days) than those without risk factors.[103] The cost of this loss in productivity on the U.S. economy was estimated at $17.3 billion. These findings also emphasize the importance of measuring physical disability and the whole HRQoL spectrum at large when the cost-effectiveness of preventive measures among the aging population is evaluated.

7.6 SOCIOECONOMIC STATUS AND CARDIOVASCULAR RISK FACTORS

The association between socioeconomic status (SES) and cardiovascular risk factors adds to the phenomenon of risk factor clustering. Persons with lower socioeconomic status as determined by income, education or grade of occupation, have been shown to have an elevated risk of cardiovascular morbidity and mortality.[104] But because lower SES is also associated with an increased prevalence of cardiovascular risk

factors, such as smoking, lower physical activity and unhealthy diet, it is unclear, how much these factors explain the difference in outcome. [105] This discrepancy is partly explained by the increased level of risk factors, but part of the mechanism is unknown. [106] Socioeconomic position was a strong predictor of disability in later life independent of a wide range of lifestyle factors and presence of diagnosed disease in the British Regional Heart study.[107] In the prospective Women's Health Study of 22.688 female participants, the traditional risk factors of CVD accounted for half of the relationship between education and CVD risk. [108] Similarly, in a Finnish study risk factors related to health behavior such as smoking, low vegetable use and physical inactivity explained 54% of the relative difference in CVD mortality between the lower and higher educational level among men. [109] Behind the other half of this gradient there may be other factors associated with lower socioeconomic status. [110] For instance, the levels of psychosocial stress and social support may be less favorable in lower social classes. There has also been shown to be a difference in the access to care according to social class and income level.[111] Both access and level of treatment and care were inferior for persons with lower socioeconomic status, according to a study examining the socioeconomic differences in the treatment of CHD in Finland.[112] Also job control is associated with occupational grade, which is also an indicator of SES. In the Whitehall Study of 17.530 English civil servants, where the socioeconomic position was based on employment grade, a lower employment status was associated with a 3.6 times higher coronary mortality than for those belonging to the professional executive grade. [113] A recent analysis of the Whitehall study cohort suggests that controlling for the classic cardiovascular risk factors would decrease the difference in mortality between socioeconomic groups by 69%.[114] The extension of this study, the Whitehall Study II, a cross-sectional analysis examining the impact of SES on SF-36 scores, found a gradient according to SES status on all SF-36 scales except Vitality. The age-adjusted difference in the Physical functioning (PF) scale between the highest and the lowest employment grade was 6.8 points. Furthermore, the PF scale decreased with age significantly more rapidly in the low SES group among both men and women. This difference among men of 60-63 years was approximately 12 points between the highest and lowest employment grade, an effect comparable to many medical conditions. This association was found also among those without pre-existing disease, suggesting that the impact of SES on physical functioning was not solely due to different status of health. [115] These findings imply that SES may be an important source of bias in clinical studies.

An association between SES and the RAND-36 scores was also detected by the cross sectional data combined from the Helsinki Health Study and the Whitehall II Study, where PCS scores were positively associated with higher education and occupational class. [116]

Additionally, less prosperous socioeconomic conditions already in childhood may have a modest but continuing influence on the risk of CHD in later life.[117] And finally, the role of persistent pathogens has recently been brought up as a possible explanation for the social gradient in cardiovascular morbidity. [118]

7.7 GENDER AND CARDIOVASCULAR RISK FACTORS

Compared to men, women have been shown to have a more favorable profile of major cardiovascular risk factors.[119] Subsequently, the average annual rates of first major cardiovascular events for women occur approximately 10 years later in life than for men, although this gap narrows with advancing age.[120] In addition to differences in lifestyle factors, part of this difference is attributed to pre-menopausal hormonal influences which exercise a protecting effect against atherosclerosis.

7.8 CHARACTERISTICS OF CARDIOVASCULAR RISK FACTORS

7.8.1 WEIGHT GAIN

7.8.1.1 Body Mass Index

The Body mass index (BMI) is a mathematical formula that describes relative weight for height. It is significantly correlated with total body fat content. BMI is defined as the individual's body weight in kilograms divided by the square of the height in meters (kg/m^2). Accordingly, a weight difference of 3.0 kg corresponds to a one-unit (kg/m^2) change in BMI for a man with the average height of 173 cm. In spite of acknowledged limitations in its ability to assess body fat regarding the distribution of muscle and bone mass, [121] the BMI index is considered suitable for distinguishing trends within overweight individuals. Since the 1980's, the BMI has been endorsed by the WHO as the standard for recording obesity statistics and it is now the most widely used measure to diagnose obesity. [122] Overweight and obesity in adults are commonly classified according to the cut-off points proposed by the WHO: overweight is defined as a BMI of 25.0 kg/m^2 or higher, obesity as a BMI of 30.0 kg/m^2 or higher, and extreme obesity as a BMI of 40 kg/m^2 or higher. The concepts of overweight and obesity are partly overlapping, because obese persons are also overweight.

7.8.1.2 Epidemiology of weight gain and obesity

Weight gain and the subsequent obesity is a growing health problem in all developed countries. By 2000, the prevalence of obesity in U.S. adults was 30.5%, compared with 22.9% in 1994. [123] In 2004, over 70% of American men and over 60% of women were overweight and 30% of both sexes were obese.[124] This trend is expected to continue: By the year 2030, 86% of American adults are estimated to be overweight and 51% obese.[125] In Great Britain the prevalence of obesity among adults has increased almost three fold from 1980 to 2002.[126] A similar trend in the obesity prevalence was observed during the 1980's and 1990's in all socioeconomic groups in Finland, where the proportion of obese adults had risen to 21% by the year 2000. [127] However, according to the latest FINRISK population survey in 2007, the prevalence of obesity has not risen during the last years; being 22% among adults aged 25-75 in 2007.[128]

BMI has been shown to increase with age, [124] also in the Finnish population, where in addition a gradient according to the birth cohort has been shown: men born between 1933 and 1962 reached a BMI of 26 kg/m^2 before the age of 40 years, whereas men born in 1913–1922 did not attain the same BMI level until around their fifties. [128] As elsewhere, also in Finland the proportion of overweight individuals is higher in lower SES groups: Data obtained by self-report in 2004-2007, indicated that 65% of men in the lowest SES were overweight and 60% of men in the highest SES as determined by education. [129] According to measured weight among the participants in the FINRISK study in 2002, the gradient of BMI was approximately 0.6 kg/m^2 and 1.8 kg/m^2 between the highest and lowest educated tertiles of the male and female populations, respectively.[130]

7.8.1.3 Weight gain, obesity and mortality

While the changes in treatments and risk factors during the recent decades have led to a reduction in cardiovascular mortality, the increased prevalence of obesity and the associated rise in the prevalence of type 2 diabetes have accounted for an increase of deaths from coronary heart disease in 2000. [131] [132] [133] In the U.S., obesity has been estimated to be the second leading cause of preventable death after smoking. [134] In 2001, about 300.000 deaths annually were associated with overweight and obesity. [135]

Overweight and obesity are associated with an increase in mortality from all causes. [136] [137] [138] In the Framingham Heart Study cohort, obesity in middle age decreased life expectancy by 6 to 7 years compared with those with normal weight. [139] This is similar to the risk associated with smoking. Overweight was associated with a 3 year reduction in life expectancy compared with normal weight individuals. Obese men had an 80% increase in risk of dying before age 70 years. A U.S. study

using the NHANES data found that obesity, but not overweight, was associated with an excess mortality of cardiovascular causes. [135] This may be in association with a recent finding that the favorable trend of diminishing risk factors has also happened among the overweight and obese individuals, as obese persons now have better CVD risk factor profiles than their leaner counterparts did 20 to 30 years ago.[140]

In a Swedish study, weight gain from age 20 was associated with increased all cause and cardiovascular mortality, as well as increased risk of non-fatal myocardial infarction.[141]

Increased body weight has also been associated with increased mortality for cancers. Overweight and obesity in the United States have been estimated to account for 20 % of all deaths from cancer in women and 14 % in men.[142] In a European study, excess body mass was estimated to account for 5% of all cancers in the European Union.[143]

Although linear relationships have been observed in some studies [144] [145], most population studies show a J-shaped association of weight and mortality. [139] [146] [147] Among them, a recent European study of over 500.000 participants showed a J-shaped association of BMI and mortality, with the lowest risk of death observed at a BMI of 25.3 for men and 24.3 for women.[148] After adjustment for BMI, waist circumference and waist-to-hip ratio were strongly associated with the risk of death. In a prospective study of over 1 million participants in the U.S., mortality risk was increased with an increasing BMI in all age groups and for both cancer and cardiovascular causes. [149] The lowest mortality rates were found at BMI between 23.5 kg/m² and 24.9 kg/m² in men and 22.0 kg/m² and 23.4 kg/m² in women; the heaviest men and women had a 40 to 80 % increase in the risk of dying from cancer. Among overweight men the cardiovascular mortality was 50 % higher and among obese men from 60% up to 200% higher.

7.8.1.4 Weight gain, obesity and morbidity

Early obesity, absolute weight gain throughout adulthood, elevated BMI and waist circumference have all been shown to be predictors of T2D.[150] [151] In a study of middle-aged British men, gaining weight more than 10% during a follow-up of 12 years almost doubled the risk of T2D. [152] In addition, obesity and overweight are associated with an increased incidence of several other cardiovascular diseases and risk factors, such as hypertension, dyslipidemia, CHD and stroke. [153] [154] [155] They are also associated with several disease states such as gallbladder disease, osteoarthritis, sleep apnoea and respiratory problems and different types of cancer, [156] [157] [158] [143] as well as overall poor health status.[159] Also weight gain from age 20-29 years was consistently associated with elevated lipoprotein levels and blood pressure in a follow- up study of eight years.[160]

Although obesity is associated with increased risk of cardiovascular morbidity, it is unclear whether this relationship is mediated by the associated risk factors, especially elevated blood pressure, glucose and lipids, or whether overweight or weight gain independently increase the atherosclerotic burden.[161] A 26-year follow-up of the Framingham study cohort showed that initial body weight predicted the incidence of coronary heart disease and death in men independent of age and other risk factors including glucose intolerance. [162] Data from the Chicago Heart Association Detection Project in Industry (CHA) study with more than 17.000 participants indicated that obesity in midlife was an independent risk factor for morbidity and mortality from T2D and CVD, when compared with those with similar risk factor status but normal weight.[163]

Also alcohol and smoking present as possible confounders when evaluating the impact of obesity on health. Alcohol consumption may be related to higher BMI.[164] Smokers may have a lower BMI but a risk of higher waist circumference[165] and more CHD. Ex-smokers have a higher body weight than never smokers, as smoking cessation may lead to weight gain in the short term. [166] [167] [168] Also, obesity and overweight are associated with lower levels of education and lower SES,[169] as well as low levels of leisure time physical activity.[170]

7.8.1.5 Weight gain and health-related quality of life

Because overweight and obesity are linked to so many chronic conditions, the impact of weight itself on HRQoL has remained unclear. Large cross-sectional studies have shown that an increasing level of obesity is strongly associated with lower quality of life.[171] [172] They also observed a J-shaped association between HRQoL and BMI. However, these studies were cross-sectional, and included also subjects with chronic conditions and diseases, which may have confounded the results. Thus the association may be reflecting the effect of medical illnesses caused by excess body weight and not the weight *per se*. Lower HRQoL seen with weight gain or obesity in these studies may be mediated by associated T2D or arthrosis, for example. In the cross-sectional study by Heo et al. of 155.989 subjects, pain appeared to be an important mediator in the association of HRQoL and weight.

Longitudinal studies on obesity and HRQoL are scarce. In the English Longitudinal Study of Aging (ELSA) participants over 65 years of age were followed for 5 years. Those with higher BMI were more likely to develop mobility problems or difficulty carrying out everyday tasks. However, excess body weight was not associated with greater risk of mortality in this elderly cohort. [173] Similarly, a study of Mexican Americans over 65 years showed a limitation of lower body active daily living (ADL) functioning for those with a weight change of over 5% during the

follow- up of two years.[174] Yet, the potential harms of obesity in older people may have been underestimated.[175]

These studies imply that excess body weight predominantly affects the physical aspects of HRQOL, and not so clearly the mental domains. In addition to increased morbidity and functional disability, obesity could be anticipated to also affect an individual's self-esteem or cause social discrimination, thus influencing the mental and social aspects of HRQoL. Nevertheless, compared to the physical components of HRQoL, the effect of obesity on emotional well-being has been shown to be only modest. Besides, even this minute effect has been suggested to be due to comorbidity rather than obesity itself. In previous studies using the RAND-36/SF-36 instrument, obesity has rather been associated with lower levels of the physical domains, such as Physical functioning, Role physical, Vitality, Bodily pain, and General health than the mental domains, [176] while overweight has been associated with impaired scores for Bodily pain.[177] In a cross -sectional study of 13.636 subjects with no chronic diseases related to obesity, the SF-12 (the shortened version of SF-36) physical component summary (PCS) scores decreased with the increasing level of obesity, while the mental component (MCS) scores were lower for subjects only at both ends of the BMI categories.[178] A study in the general Swedish population of 5.333 subjects found that the PCS scores of SF-36 deteriorated from 52,0 points for subjects with normal weight to 42,6 points for subjects with BMI over 40 kg/m^2. [179] No change was seen in the MCS. The obese middle-aged male participants in this study reported significant impairments in the scales of Physical functioning and General health. However, concomitant diseases were not accounted for in this cross-sectional study.

In a study of Dutch individuals, using SF-36 to measure HRQoL, overweight and obesity were inversely related to the Physical functioning scale.[180] In another cross-sectional study of 6.318 Taiwanese participants, only the Physical functioning scale was found significantly poorer for those with BMI ≥30 kg/m2 compared to non-obese individuals. No significant differences were found for overweight subjects. [181]

In a cross-sectional analysis of the data of the Nurses' Health study of 56.510 normal and overweight women aged 45 to 71 years, the women with BMI 30 to 35 kg/m^2 reported approximately 10% lower scores (from 5.6 to 9 points) for the SF-36 scales of Physical functioning, Vitality and Pain compared with women with BMI 22 to 23.9 kg/m^2. BMI was also a predictor of impaired work ability in this study population. [182]

There are few studies on the impact of weight gain on HRQoL and they have mainly included obese subjects. An exception is an analysis of the data of the Nurses' Health study, [183] where 40.098 women were followed for 4 years. Lean women who gained more than 9.0 kgs during the 4-year follow-up period experienced significant reductions in the SF-36 scales of Physical functioning, Vitality and Bodily pain compared with woman with stable weight, regardless of age or baseline BMI

levels. The decine was 6.9 points in the scale of Physical functioning compared with woman with stable weight. In comparison, at the same time, the respective decline for smoking women was 2.5 points.

Using the data of the 6.895 male and 3.413 female British civil servants in the Whitehall II study, Stafford et al. [184] investigated the impact of weight gain from the age of 25 on for 49 years, controlling extensively for confounders. They found no association between weight gain and the Physical functioning score of SF-36 in men. In contrast, women demonstrated a decline in physical HRQoL according to fluctuations in weight. The reason for this gender difference remained obscure.

7.8.2 CHOLESTEROL

7.8.2.1 Cholesterol levels and mortality

It is widely recognized that elevated serum total cholesterol is a major and modifiable risk factor for cardiovascular disease. [185] In different clinical studies the relationship between serum cholesterol and coronary heart disease death rate has been shown to be continuous, graded, and strong. [186] A 1% decrease in LDL cholesterol concentration reduced the absolute risk of ischemic heart disease by 1-2 %,[187] also in a recent meta-analysis,[188] but even stronger effects have been reported: Law et al. suggested a 30% reduction in ischemic heart disease at age 60, instead of 20%, for a 10% reduction in serum cholesterol concentration.[189] In another study using data from cohort studies, Law et al. found that a 10 % reduction in serum cholesterol level at the age of 40 years reduced the relative risk for CHD by 50% at age 40, whereas the same 10 % lowering of cholesterol begun at the age of 70 years reduced the risk only by 20 %.[190] This highlights the importance of early intervention for maximum benefit later in life. A meta-analysis of randomized trials of cholesterol lowering showed a 19% reduction in coronary mortality for every 1 mmol/L of LDL lowered regardless of the initial lipid levels during a period of 5 years. [191] As there is no threshold in the relationship between serum cholesterol and CHD, the increased risk is not confined to the highest levels of serum cholesterol, but in a continuously graded manner affects a great majority of middle-aged men in developed countries. In the Multiple Risk Factor Intervention Trial (MRFIT), a study of 356.222 men with 6 years of follow-up, serum cholesterol levels 4.65 mmol/L or greater were associated with 46% of the excess deaths that were due to cardiovascular diseases. A recent report on the 25-year results of the extension of the MRFIT study only confirms these findings. [192]

Furthermore, another recent meta-analysis [193] of 61 cohorts and 900.000 individuals, with an average follow-up of 13 years was on level with the findings of the MRFIT trial; Cholesterol level was a strong predictor of CHD in all age groups

and regardless of other risk factors of hypertension, smoking or BMI, which the MRFIT data was lacking. Risk of CHD mortality was about 50 % lower for every 1 mmol/L reduction in total cholesterol in early middle age (40-49 years) and about 15% lower in the old age group (70-89 years). However, the absolute excess risk was greater with older age.

Although the Honolulu Heart Program [194] reported increased mortality for the participants with very low cholesterol, the suggested J-shaped association of cholesterol and mortality seen in cross-sectional studies has subsequently been suspected to be due to underlying disease. [195] [196] Terminal or otherwise serious health states may lead to diminished absorption or increased synthesis of cholesterol and thus lower serum cholesterol levels.

During the last decades, there has been a favorable trend in the levels of serum cholesterol in the developed countries. In the U.S. the age-adjusted serum cholesterol levels among adults aged 20–74 decined from 5.74 mmol/L in 190–1962 to 5.25 mmol/L in 1999–2002. [197] A much greater decline from 7 mmol/L to 5.3 mmol/L since the 1960's has taken place in Finland.[198] The latest report of the FINRISK 2007 survey implicates that this favorable trend is continuing. However, compared to other industrialized countries both the serum cholesterol levels and intake of saturated fats are still at a higher level in the Finnish population. [199]

7.8.2.2 Cholesterol levels and health-related quality of life

The association of cholesterol levels and HRQoL have not been widely examined. With the prevalent use of statins in the population, examining the relationship between natural levels of cholesterol and HRQoL would not presently be feasible or ethically sound. Thus this can only be investigated in a cohort of long term follow-up started well before the extensive use of lipid lowering medication. Since the introduction and subsequent wide clinical use of statins to effectively lower cholesterol in patients with risk of cardiovascular disease, much interest has also been directed to the question whether lowering cholesterol might produce harms.

The association of cholesterol and HRQoL has mainly been studied in conjunction with other risk factors or in some special patient groups. A special cohort of 2.531 participants in the Framingham Heart Study, those who survived to age 85, was followed from mid-age for morbidity free survival.[200] The prevalence of validated medical outcomes, vascular diseases, dementia, and cancer were used instead of a HRQoL instrument to assess quality of life. Every decrease of 1 mmol/L in baseline cholesterol value increased the survival to age 85 free of major comorbidity by 18%.

There are hardly any studies examining the association of natural cholesterol levels using a validated HRQoL instrument. A cross-sectional study of 284 cardiac patients with dyslipidemia reported better physical health than those without dyslipidemia.[201]

A recent study of 37 Finnish patients with familial hypercholesterolemia, most of them with CV disease, did not show any differences for the RAND-36 scales compared with the general population. [202]

7.8.3 ALCOHOL

7.8.3.1 Alcohol and mortality

Excessive alcohol consumption causes well-known health hazards and societal ills. [203] As a risk factor, alcohol related diseases rank fifth on the WHO's list of global burden of disease, causing 3.2% of global mortality. [87] In an estimate by WHO for the year 2030, alcohol use disorders are expected to rank number four on the list of the leading causes for loss of DALYs (4.7% of total DALYs lost) in countries of high income. [204] In Finland, an alcohol-related disease or accidental alcohol poisoning was the leading cause of death for both working-age (ages 15 to 64 years) men and women in 2007. Alcohol-related causes were responsible for 18.7% in men and 11.5% in women of all deaths in this age-group. Moreover, the number of alcohol-related deaths increased by 8.6 % from 2006.[205]

On the other hand, several studies suggest a dose-dependent, J-shaped relationship between alcohol consumption and cardiovascular mortality. Compared to abstinence or heavy drinking, favorable effects of moderate alcohol consumption (usually defined as 1-2 drinks daily in men and 1 drink daily in women) especially on cardiovascular diseases and mortality have been documented in numerous studies. [206] These include the prospective American Cancer Society's Cancer Prevention Study I, with 18.771 deaths from coronary heart disease, [207] as well as several meta-analyses [208] [209]. These studies show a consistent reduction of about 20% in mortality of cardiovascular causes in those participants who consume about one drink a day compared to abstainers. However, this benefit has not been established in all studies. [210] [211] In the British Heart Study, 70% of middle aged non-drinking male participants were in fact ex-drinkers, with a high rate of obesity, smoking, hypertension and other illnesses. [212] Furthermore, this follow-up study found that many participants with a heavy drinking pattern became abstainers or rare drinkers when diagnosed with a heart disease or other illness during the follow-up. This finding challenges the J-shape association of alcohol and mortality, as well as that of quality of life, and supports the sick quitter hypothesis as an explanation for the negative findings for the abstinence group. This concerns especially cross-sectional studies, but also those prospective studies, where the abstinence group has not been extensively evaluated at baseline.

At the metabolic level ethanol has been shown to have a cardio protective effect mediated via an increase in HDL-cholesterol and positive changes in glucose metabolism and hemostatic factors. [213] Drinking more than about one drink daily does not seem to give further protection, [214] possibly because the protective effects are overtaken by higher blood pressure and other negative consequences on the lipid and glucose metabolism [215]. Moderate alcohol consumption has also been associated with less dementia and better cognitive function. [216] [217] Consequently, moderate alcohol consumption could even be advocated for preventive purposes in middle-aged and old people. However, here too, there are opposite views, because observational studies cannot distinguish whether moderate drinking is associated with other lifestyle habits beneficial for cardiovascular health. [218] Moderate users may be protected by healthier diet, less smoking, better social support or better health status ("the healthy user bias"). [219] [220] Furthermore, the incidence of cardiovascular disease is lower in higher social classes.

Thus, although many studies have shown that moderate alcohol use has a beneficial effect on metabolic factors mediating CVD, and although moderate alcohol consumption reduces the incidence of CVD in observational studies, the fact whether this is a cause–effect relationship, as well as the long-term benefit of moderate alcohol use remain in dispute. To settle this issue, a randomized controlled trial would be needed. However, it would be ethically as well as technically difficult to conduct such a trial with alcohol. As it is, there are many challenges for further studies: Alcohol consumption is usually a life-long habit, and the health effects should also be considered over the lifespan instead of a short follow-up time, and data of lifetime drinking habits are required. Controlling for confounders, especially social class, is important in observational studies. [221] Also patterns of drinking, for instance binge drinking, should be recorded.

7.8.3.2 Alcohol and health-related quality of life

In the light of the disagreement over the benefits of moderate alcohol use, quality of life is a relevant addition to the endpoints for a follow-up study of overall alcohol effects. For example, a 5 to 10-year postponement of coronary heart disease may not necessarily be worth the possible negative effects on health later on. Therefore, it is important to consider also other outcomes in connection with alcohol consumption.

Despite the many effects that excessive alcohol consumption causes on the individual, family and society, the research on alcohol use and alcoholism has only recently included HRQoL as an outcome along the more traditional measurements.[222] This is complex, because there are several factors confounding this association. Alcohol causes many illnesses such as cardiovascular, liver and

gastrointestinal diseases as well as neurological and psychiatric disturbances. [223] It is also associated with lower socioeconomic status and further related to poorer work ability and problems in social life.[224] Gutjahr et al. identified over 60 health consequences attributed to alcohol consumption. [225] Also smoking is more common among those with excessive alcohol consumption [226] contributing to the difficulty of determining the association of alcohol consumption and HRQoL.

Another confounding element is that the habits of alcohol consumption vary from abstinence at one end to alcoholism at the other, while similar average weekly consumption may include different patterns of drinking such as binge drinking (generally defined as consuming five or more alcoholic drinks on one occasion [227]) or low- to moderate dose consummated daily. This variation may depend on the person's cultural background, making the interpretation of the outcomes at population levels further intriguing.

The relationship between alcohol and HRQoL has mainly been studied in the field of alcohol dependency or in evaluating the treatment of alcoholism, and only few studies have examined the association of light or moderate use and HRQoL. HRQoL among alcoholics has been shown to be lower both during periods of excessive use and after treatment. In a study of 1.333 primary care patients Volk et al. found that those who fulfilled the criteria for alcohol dependence scored lower points for all eight SF-36 scales. Patients who consumed alcohol in a frequent, low-quantity pattern showed better overall HRQoL than persons in other consumption groups. [228] Using the vast cross-sectional data of the Behavioral Risk Factor Surveillance System (BRFSS), Okoro et al. found that frequent binge drinking (three or more times a month) was associated with significantly worse HRQOL. [229] This was consistent with the results of Volk et al. who reported that binge drinkers and those with a frequent, high-quantity drinking pattern had lower scores for the SF-36 scales of Role functioning and Mental health.

In a review the HRQoL of alcohol-dependent subjects was shown to be very poor, but improved as a result of abstinence, controlled or minimal drinking.[230] Cutting down alcohol consumption by 30% or more was associated with an improvement of 3.3 points in PCS scores compared to those with a less than 30% decrease in consumption during a one year follow-up. [231] In a study of twins, the alcoholic twins reported significantly lower scores for all SF-36 scales than their non-alcoholic counterpart twins. However, after adjusting for several confounding factors, such as physical and psychiatric problems, nicotine and drug dependency, marital status and income, only the Vitality scale of SF-36 remained significantly worse among the alcoholic twins, suggesting that the differences in HRQoL were attributed more to other factors than to alcohol. [232]

Dawson et al. used SF-12 to analyze the changes in HRQoL of 22.245 persons with an alcohol use disorder during a follow-up of three years. [233] Those who developed a

dependency, showed significantly lower mental well-being, and those who reached remission from dependency, showed better scores as measured with the MCS of SF-12. The results support the sick quitter hypothesis, which suggests that the abstinent group especially in cross-sectional studies may include persons who have stopped drinking due to factors that lower their quality of life.

Nevertheless, there are studies which support a true J-shaped association between alcohol use and HRQoL. In a study of older patients, those who reported drinking alcohol, but who did not report problem drinking, had consistently better survival and health status as measured with SF-36 than those who did not drink and those who reported problem drinking.[234] In a longitudinal study of 12.000 older Australian women, a J-shaped, dose-dependent association was found between physical quality of life measured with SF-36 PCS accounting for death, with non-drinkers reporting lower physical HRQoL than moderate drinkers. [235]

7.8.4 SMOKING

In 2007 in Finland, 26% of men and 17% of women aged 15-64 were smoking daily. [236] In the age group 25 to 44 years 30% of men were smokers. The prevalence decreases with age, partly because of the higher mortality of smokers and partly because quitting among men has increased since the 1970's. [237] The prevalence of daily smokers decreases also with increasing education. The proportion of smoking men was 17% in the highest educational group as opposed to 37% in the lowest. The difference in smoking prevalence according to educational level has broadened in the age group of 24-65 years in the Finnish population. [130]

7.8.4.1 Smoking and mortality

Over 50 years ago, Doll et al. first showed that smoking can cause lung cancer. [238] Since then, numerous studies have demonstrated the various ill effects that the use of tobacco has on health by causing especially vascular, neoplastic, and respiratory diseases. Smoking has a harmful effect on almost every organ in the human body and it is also the most powerful risk factor for atherosclerosis. [239] In men, smoking has been shown to shorten life by 7-10 years. [239] [240] [241] Worldwide, smoking is the second leading risk factor for all-cause death from any cause, with almost 5 million deaths in 2000, about half of them in the developing countries. [242] In the U.S. smoking is the single greatest cause of preventable morbidity and mortality. [243]

7.8.4.2 Smoking and health-related quality of life

Although previous studies have shown that a low cardiovascular risk factor profile in middle age supports better HRQoL later in life,[244] the effect that lifetime smoking *per se* has on the HRQoL has not been clearly demonstrated. The problems in evaluating the association of smoking and HRQoL are similar to that of alcohol. Smoking is linked to many confounding factors related to gender, secular lifestyle, education and social class. [245] In addition, for some people smoking is a life-long habit, and some may quit smoking. The time since quitting is difficult to record in studies, and relapses are common. Furthermore, the reasons for cessation range from social factors to ill health. These confounding factors may be difficult to control for in studies of the general population.

Besides the fact that smoking itself is strongly associated with several serious diseases, it is also linked to factors that may affect the quality of life, such as poorer nutrition [246] or lower socioeconomic status [247]. Thus it would be plausible that smoking also diminishes the health-related quality of life in the long-term. However, dying earlier does not necessarily mean worse HRQoL, especially during the last years of life. Living longer may mean more years of disability and lower HRQoL during the extra years gained: If non smokers live longer they also have more time to develop coronary heart disease or other chronic diseases causing disability and worse HRQoL. At the end of their life non-smokers will have lived longer with cardiovascular disease.[248] On the other hand, non-smokers have been shown to live with less disability. [249 250] Furthermore, it is also possible that smoking and nicotine may have some beneficial effects, such as relieving psychological stress or preventing Parkinson's or Alzheimer's disease, which may have a favorable effect on the quality of life of smokers.[251]

The impact of smoking on HRQoL has been studied in cross-sectional studies of the general population, [252 253 254] which, however, cannot examine causality or take death into account. Shorter follow-up studies have been made in multiple disease states showing the benefits of non-smoking in these subgroups. [255 256 257]

However, few prospective studies have examined the impact of long-term smoking on HRQoL in the old age. An 8 year follow-up study of older people showed a strong relationship between smoking and worse quality of life and years of healthy life lost.[258] Likewise, few follow-up studies have investigated the HRQoL of ex-smokers. Previous studies have reported improvements in HRQoL after smoking cessation. A short follow-up study showed that cessation had a positive effect on HRQoL in nicotine-dependent smokers. [259] A 4-year follow-up demonstrated improvements in the SF-36 scores of Mental health, Vitality and General health of ex-smokers. [260] However, in a study of smokers with atherosclerotic disease, cessation did not show benefit on HRQoL.[261] Another cross-sectional study demonstrated moderate differences in smokers' and ex-smokers' perceived quality of life, with

mean differences from 3.9 points in the Physical functioning scale up to 5.3 point difference in the General health scale of RAND-36. [253]

According to a recent finding in the Nurses' Health Study, PCS and MCS of SF-36 were significantly lower for female smokers, compared with never- and ex-smokers. However, after 21 years of smoking, cessation did not bring an improvement in HRQoL among women.[262]

7.8.5 RISK FACTOR CLUSTERING

7.8.5.1 Risk factor clustering and mortality

As cardiovascular risk factors are often present in the same individual, the overall risk factor status may vary from low risk to high risk. [263] In the Framingham Heart Study low levels of major cardiovascular risk factors in middle age were beneficial for overall survival and morbidity-free survival to age 85. [264] Based on the very large cohorts of the MRFIT study and CHA study, Stamler et al. [265] demonstrated that mortality was much lower for individuals with favorable levels of cholesterol and blood pressure, who did not smoke and did not have diabetes. For the low-risk group of men, the life-expectancy was 9.5 years longer. Accordingly, a study of 34.192 California Seventh-Day Adventists suggested that healthy lifestyle increased life expectancy up to 10 years. [266]

In spite of the many methodological problems in quantifying and accurately relating the actual causes of deaths to modifiable lifestyle factors, smoking and a low diet quality and sedentary lifestyle were shown to contribute to the largest number of deaths in the U.S. in 2000. [267]

In the large Nurses' Health Study, 55% of deaths during the 24 years of follow-up were attributed to the combination of smoking, overweight, low physical activity, and poor diet.[268] Similar findings have also been made in a smaller cohort in Europe. [269] Beneficial levels of major cardiovascular risk factors have been shown to lower age-specific mortality also in the Finnish population. [270] [271] Wannamethee et al. investigated the association between smoking, physical activity, alcohol consumption, and BMI and the likelihood of 15-year survival free of coronary heart disease, stroke, and diabetes in a cohort of 7.142 middle-aged men in the British Regional Heart Study. [272] According to the findings of this study, a 50-year old man, who is obese, smokes and has low physical activity, has only a 42% chance of surviving 15 years free from CVD or T2D compared with the 89% chance of a 50-year old man free of these risk factors.

7.8.5.2 Risk factor clustering and health-related quality of life

Assessment of the impact of concurrent cardiovascular risk factors on cumulative disability or well-being over the lifespan is difficult because the trends in risk factors have been in transition. While other major risk factor levels have decreased in the population, the prevalence of obesity has rapidly increased. Besides, there may be different trends according to ethnicity or nationality. Defining the impact of different combinations of lifestyle factors (such as smoking or low physical activity), physical elements (e.g. excess body weight or hypertension) and metabolic risk factors (e.g. cholesterol or diabetes) is complex because there are different cause – relationships involved. The choice of risk factor combinations in different studies is subsequently diverse. Furthermore, age, socioeconomic status or educational level all may have a confounding effect on the results.[273]

The effect of different constellations of combined lifestyle or risk factors on the health-related quality of life has effectively been studied only during the last decade. The first longitudinal study to examine the relation between cumulative disability or mortality and lifestyle factors was a study of 1.741 former university alumni with a follow-up from the average age of 43 years to the age of 75 years. [274] A disability index was created by assessing eight concepts of active daily living. Smoking, higher BMI, and a low exercise pattern predicted mortality and initial disability at a younger age. The disability index for the high-risk subjects who died was double compared with the low-risk subjects during the last years of observation.

The first study to examine the effect of cardiovascular risk factors on HRQoL in a broader fashion beyond physical disability, i.e. also the mental and social aspects, was published in 2003, when over 7.000 subjects in the large CHA study had been followed-up for 26 years. [245] SF-12 was used as the HRQoL instrument. Participants with favorable levels of all major CVD risk factors in middle age had a significantly better HRQoL and less infirmity in older age. The HRQoL decreased with the growing number of risk factors; the individuals with a low risk for CVD scored the highest points for physical, mental, social functioning and disease-free outcomes. In men, the largest decline was seen in the Physical functioning scale: 7-10 points between men with two or more CV risk factors compared with those with no risk factors at baseline. The differences in the Mental health scale were not statistically significant. Also the health care costs were significantly lower for the group free of CV risk factors according to an earlier analysis of the CHA study data. [275]

Risk factors seem to still have an effect later in life, when selection has already occurred. Among the prospective cohort of the Physicians' Health Study, 2.357 healthy older men (average age 72 years at baseline) were assessed 16 years after baseline (mean age 86 years) with the PF scale of the SF-36 questionnaire to investigate the impact of risk factors on their functional status and well-being. [276] The men were then followed yearly until they died or reached the age of 90, up to 26 years. During follow up, smoking, diabetes, obesity and hypertension

significantly reduced the lifespan. Clustering of these risk factors attenuated the risk. The probability of surviving from age 70 to 90 years was less than 10 % for those with concurrent risk factors compared to 54% for those men with no risk factors. Among those who lived to age 90, the low risk group scored 11.4 points more on the PF scale and reported 3.2 points better mental well being on the scale of Mental health than those with several risk factors.

7.9 PSYCHOLOGICAL WELL-BEING

Parallel to WHO's definition of health, [12] also mental health is more than just the absence of mental illness. This is pointed up in the definition of psychological well-being by WHO: *"... a state of well-being in which the individual realizes his or her own abilities, can cope with the normal stresses of life, can work productively and fruitfully, and is able to make a contribution to his or her community".* [277] In this characterization the positive side of mental health, psychological well-being, is the basis for the individual's successful functioning in his social environment.

7.9.1 DEPRESSION AND CARDIOVASCULAR DISEASE

While mental health is much affected by socioeconomic and environmental factors and is thus enhanced at the population level mainly through social interventions, also cardiovascular risk factors have shown to play a part in psychological health. There is an established link between depression and cardiovascular disease. Both conditions are often seen in the same patient and depressive symptoms in patients with cardiovascular disease have been shown to worsen their prognosis. [278] A large U.S. population study of eight years duration showed a 51% increased total mortality for persons with depression compared with those without depressive symptoms. Their CHD mortality was increased 1.3 to 1.5 fold, and over two-fold in depressive persons with diabetes. [279] During 18 years of follow-up of over 12.000 men with high CV risk participating in the MRFIT study, the men with the greatest depression at baseline had a two-fold increased risk of mortality from stroke compared to those with no depressive symptoms.[280] In a Finnish population sample, all-case mortality was increased in subjects with depression, whereas an increase in cardiovascular endpoints was seen only in women. [281] However, the direction of causality and plausible mechanisms of the association between depression and cardiovascular disease have remained obscure. There is also only limited data proving that treating depression could improve cardiovascular outcomes: Medical treatment of depression had only a modest effect on cardiovascular outcomes in patients with CHD. [282]

The prevalence of depressive symptoms among older adults varies between 8-16 %, while estimates of the prevalence of major depression in late-life have widely been around 1-4%. [283]The etiology of depression may depend upon the age of onset. Vascular lesions in the brain have been suspected to be an important etiological factor for depression presenting later in life, and thus also the clinical symptoms may be different between early-onset and late-onset depression. [284]Although depression is less frequent in old age than earlier in life, depression is a significant factor affecting the HRQoL of older people. In a cross -sectional study, depressed participants over 60 years of age showed significantly lower scores for five of the eight SF-36 scales (General health, Mental health, Role emotional, Social functioning and Vitality) compared with norms for older individuals. [285] Several studies have also found a link between depression and physical functioning. In a follow-up study of four years' duration of older participants, depressive symptoms predicted a decline in measured physical performance. [286] However, even in longitudinal studies the direction of causality is not clear for the functional decline seen in depressive patients, because disability may induce depression and on the other hand, depressed participants may report their physical functioning lower than non-depressive controls. [283]

7.9.2 POSITIVE HEALTH STATES

There has been growing clinical and research interest in positive psychological well-being, because positive feeling states appear to have consequences that are independent of negative states. [287] The distinction between negative and positive affect was first introduced by Bradburn in 1969. [288] He concluded that an individual's psychological well-being depends on the independent dimensions of positive and negative affect. According to this definition, positive affect is not simply the opposite of negative feeling state.

Because psychological well-being depends besides health on many genetic, social and economic factors, there are consequently many variables attached to the concept of positive affect. [289] Among the positive feeling states, happiness and life satisfaction have been identified as central indicators of psychological well-being and functioning. [9] However, these concepts are loosely defined and are often seen to be used interchangeably with subjective well-being in the medical literature.

Positive states are also related to physical health: Positive affect has been associated with fewer strokes, [290] life satisfaction was related to long-term mortality among healthy adults,[291] and positive life orientation predicted subsequent survival in old people [292]. The processes that underlie these effects are not clear. Positive emotions may be a life-long trait and promote a health-conscious lifestyle. Furthermore, a study showed that positive affect in middle-aged individuals was

directly related to biological processes (cortisol output, heart rate and fibrinogen stress response) associated with beneficial health effects. [293] On the other hand, positive affect may also be modulated during the life course. Nevertheless, as part of mental health, positive emotional states are related to a key dimension in HRQoL. Subsequently increasing happiness among the growing geriatric population has been identified as an important aim in public policy. [87]

8 AIMS OF THE PRESENT STUDY

These studies were performed to examine the impact of major modifiable cardiovascular risk factors (weight gain, cholesterol, alcohol consumption, smoking and combined risk factor status) present in middle age on the health related quality of life in old age, with account for mortality and several confounding factors among the cohort of the Helsinki Businessmen Study.

I The aim of substudy I was to investigate whether gaining weight since the age of 25 years to middle age predicts health-related quality of life in old age.

II The aim of substudy II was to examine how the amount of alcohol consumed in middle age affects the health-related quality of life in old age, with mortality taken into account.

III Substudy III aimed to study the effect of serum cholesterol in middle age on the HRQoL in old age.

IV The effect of cigarette smoking in midlife on the HRQoL in old age was investigated in substudy IV.

V In substudy V clustering of cardiovascular risk factors was identified in the cohort in middle age to investigate their influence on HRQoL later in life.

VI Substudy VI aimed to further examine how cardiovascular risk of men in midlife is associated with mental aspects of HRQoL, specifically the negative and positive affect in old age.

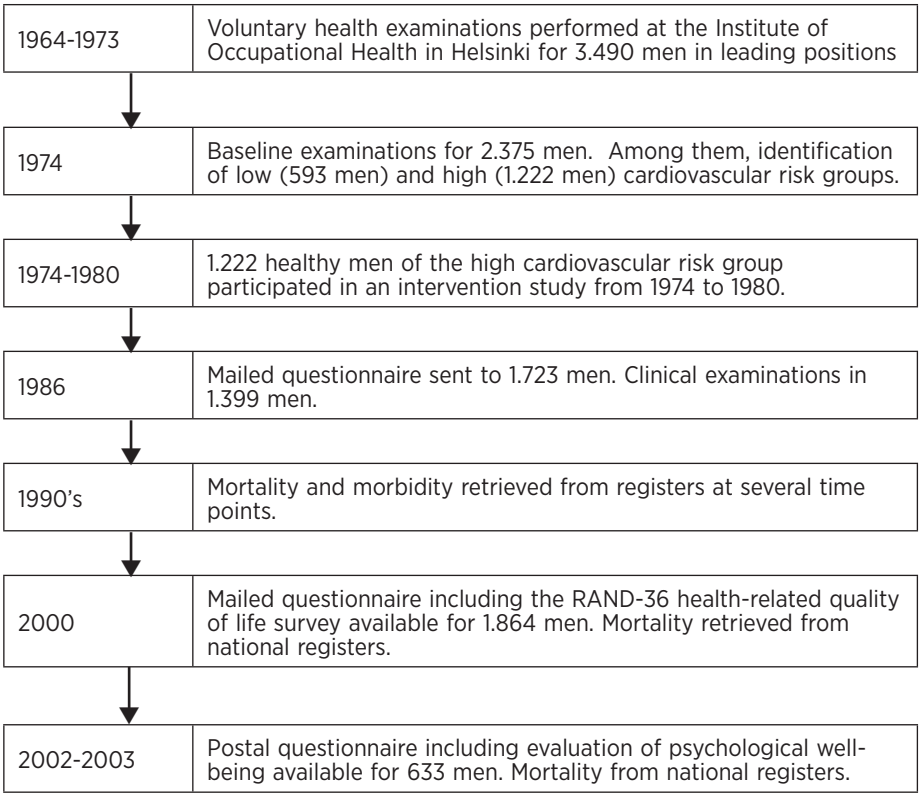
9 DATA AND METHODS

9.1 THE HELSINKI BUSINESSMEN STUDY

The current thesis project is part of a prospective study called the Helsinki Businessmen Study. The data gathered from the participants who took part in the examinations between 1964-1973 (median year 1968) offer the basis for the studies presented in this thesis. The schedule of the Helsinki Businessmen Study from the 1960's to 2003 is presented in Figure 1. A more detailed timeline for the study is summarized in Appendix C.

Since the data for cardiovascular risk factors has been collected at different time points and as the availability of data is different for each risk factor, the follow-up time for the impact of individual cardiovascular risk factors varies, as outlined for the respective substudies in Table 7.

Figure 1. Timeline of the Helsinki Businessmen Study



9.2 BASELINE EXAMINATIONS IN 1964-1973

Since 1964 the Institution of Occupational Health in Helsinki performed voluntary health examinations aimed at men in leading job positions. Up to the year 1973, 3.490 men took part in these examinations, which were then repeated with intervals from 2 to 5 years. At that time occupational health care was not customary in Finnish companies. The men were mostly business executives or managers in different companies mainly in the field of industry or commerce. They were born in 1919-1934, and the mean age in 1974 was 47.8 years (SD 4 years). The constitution of these health checks are presented in Table 1.

Table 1. The composition of the health evaluations performed between 1964 and 1973 (median year 1968):

Assessment	Contents
Clinical examination	• performed by a physician • height and weight measured • blood pressure • smoking status
Laboratory examinations	• serum cholesterol • serum triglycerides (from 1969 onwards) • blood glucose one hour after a glucose load (1 g/kg of body weight of glucose orally)

Of the original examinations of 3.490 men, risk factor levels are available for 3.313 men, 95% of the original study population.

This cohort was not originally created for scientific purposes, but it was later discovered that the socioeconomic similarity of the participants offers an appropriate basis for evaluating the significance of cardiovascular risk factors on subsequent health status. Consequently some observational studies have been performed using the data gathered from this cohort.

9.3 BASELINE EXAMINATIONS IN 1974 IN GENERAL (MIDLIFE EXAMINATION)

The first scientific investigation of this cohort was performed in 1974, when associations between baseline electrocardiographic findings and cardiovascular risk factors and coronary heart disease were examined in 2.821 participants. [294]

In 1973-1975 (mainly in 1974) the men were approached in order to find healthy participants with cardiovascular risk factors for a primary prevention study. A

mailed questionnaire and an invitation to have laboratory samples and an ECG taken were sent to all men who had participated in the health examinations since 1964. The contents of the questionnaire in 1974 are presented in Table 2.

Table 2. The composition of the questionnaire in 1974.

Past and current diseases and medication
Cardiovascular risk factors and lifestyle

• Smoking status
  • never smoker/ex-smoker/current smoker
  • number of cigarettes smoked/day
  • use of cigar/pipe

• Alcohol consumption
  • preference: beer, wine or liquor
  • consumption/week

• Self-reported current health and physical fitness   • 5-step scale: ”very good”, ”good”, ”fair”, ”poor”, ”very poor”

Based on the self-reported questionnaire, the presence of chronic diseases, regular use of medication, abnormal laboratory results and ECG findings were used as exclusion criteria for the primary prevention study (Table 3).

Table 3. Exclusion criteria for the primary prevention study in 1974.

Hypertension	• SBP ≥ 200 mm Hg and/or DBP ≥115 mm Hg (values exceeded both in the self reported questionnaire and at clinical examination). • medication for hypertension • secondary hypertension
Cardiovascular disease	• History of myocardial infarction • Angina pectoris according to the Rose questionnaire[295] • ECG changes, classified according to the criteria defined by the Minnesota Code [296] : • CHD • Conduction abnormalities • Cardiac arrhythmia, disturbances of cardiac rhythm • History of or clinical cardiomyopathy • History of valvular disease, III-IV degree systolic murmur or diastolic murmur on clinical examination • Heart failure: treated or clinically present
Cerebrovascular disease	• History of TIA or stroke (cerebral hemorrhage or ischemic stroke) • Unilateral symptoms or findings of hemiparesis on clinical examination
Diseases of the kidneys	• Renal failure (S-creatinine ≥ 150 umol/L) • Renal disease: proteinuria, pathological findings in sediment or urography
Metabolic diseases	• Medical treatment for diabetes • Uncontrolled diabetes (fasting blood glucose ≥ 10 mmol/L) • Medical treatment for hyperlipidemia
Psychiatric disorders	• Psychoses • Severe neuroses • Alcoholism
Malignant diseases	

Of the original cohort, 68 men had died before 1974. Furthermore, 867 did not respond or refused to take part in the study. Subsequently, according to the medical history and cardiovascular risk profile presented by the results of these questionnaires and laboratory and ECG findings, the cohort could then be divided into 5 groups:

1) Men who reported to be healthy, with no cardiovascular risk factors above the predefined levels and no symptoms or signs of cardiovascular disease (= the low risk group, n=593).
2) Men who reported to be healthy, but had at least one predefined cardiovascular risk factor (= the high risk group, n=1.222).

3) Those with known chronic disease or medication as described above (n= 563)
4) Those who refused or data is otherwise not available (n=867)
5) Dead (n=68)

The group of the 1.222 men who were healthy and who had at least one cardiovascular risk factor, was then divided into two groups for an intervention trial to investigate the effect of intensive treatment of cardiovascular risk factors in 612 men, compared to a control cohort of 610 men who did not receive any special action for their risk factors. For this purpose, a clinical examination was performed on all 1.222 participants and this included the procedures presented in Table 4.

Table 4. Measurements for the 1.222 men, who were healthy, but had at least one cardiovascular risk factor in 1974.

Variable	Measurement
Blood pressure	measured with a mercury sphygmomanometer in the sitting position after a 10-min rest.
Heart rate	calculated from the resting ECG
Cholesterol and triglycerides	measured by standard methods in the fasting state
Blood glucose	measured in the fasting state and one hour after a glucose load (1 g/kg of body weight of glucose orally).
Smoking status	determined on the basis of a self-reported questionnaire (number of cigarettes/day)
Alcohol consumption	assessed with a self-reported questionnaire (beer, wine, and liquor separately), calculated as grams of ethanol per week.
Weigh	measured. *

** In 1974, relative body weight (%) calculated as body weight (kg) * 100 divided by height (cm) minus 105), was used to characterize overweight. However, body mass index (BMI), calculated as weight (kg) divided by height (meters) squared was used in the subsequent analyses.*

The results of this intervention trial from 1974 to 1980 were published in 1981 and 1985. [297] [298]

9.4 EXAMINATIONS IN 1986

A third scientific evaluation was performed in 1986, when the changes in the risk factors during follow-up were recorded and the effect of the intervention program from 1974 to 1980, six years after the final visits was re-evaluated.[299] For this a mailed questionnaire was sent to those participants (n= 1.723) who were healthy in 1974 and alive in 1986. 1.399 men (82%) replied, although the responses to the questionnaire were not all complete. Smoking status and alcohol consumption were assessed by the questionnaire. The men were also asked to have their blood pressure, weight and waist circumference measured, as well as blood samples and ECG taken at their local health care provider. Cholesterol values were gathered in 1.246 (73%) men, HDL- cholesterol in 1.241, triglyceride in 1.236 and glucose values in 1.215 participants.

9.5 FOLLOW-UP OF MORTALITY AND MORBIDITY DURING THE 1990'S

Mortality and morbidity of the initial cohort and the groups which were identified in 1974 have been followed up using national registers during the 1990's. These results have been published previously. [300] [301] [302]

9.6 THE 2000 SURVEY (LATE-LIFE EXAMINATION)

In 2000, a mailed questionnaire was sent to all 2.286 survivors of the original cohort of 3.490 men, re-mailed once for non-respondents and 1.864 (88%) responded. The questionnaire included the variables presented in Table 5.

Table 5. The composition of the questionnaire in 2000

• current diseases including cardiovascular diseases and diabetes
• alcohol consumption
• physical activity
• weight
• the latest measured BP value
• current smoking status
• the Finnish version of the RAND-36-Item Health Survey 1.0

Because a substantial proportion of men had died by the time of the RAND-36 evaluation in 2000, the technique described by Diehr et al. [66] to account for deaths when assessing health-related quality of life was used for substudy III. This technique produces logistic regression coefficients to derive new PCS and MCS values which account for death and estimate the probability of being healthy in the future. Being "healthy" is defined as being in the top 75% of the reference population for the PCS and MCS. Death is coded as zero. This method was employed to obtain the transformed PCS and MCS values presented in the substudy III of this thesis.

The summary measures of RAND-36 have not been validated in the Finnish population. Therefore, the general 1998 U.S. population norms are used as reference for the PCS and MCS scores in the substudies of this thesis.

9.7 THE 2002-2003 SURVEY OF NEGATIVE AND POSITIVE AFFECT

In 2002-2003, another mailed questionnaire survey was sent to the surviving participants (n=872) (re-mailed once for non-respondents) and at this point 73% (n=633) responded. The questionnaire included partly the same items as the 2000 survey (symptoms and diseases, current medications, present weight). In addition there were also several questions about attitudes towards life.

Table 6. The composition of the 2002-2003 questionnaire of negative and positive affect (response categories are presented in parenthesis).

• Are you satisfied with your life? (yes/no),
• Do you have zest for life?(yes/no),
• Do you feel needed? (yes/no),
• Do you have plans for the future? (yes/no),
• Do you suffer from loneliness? (seldom or never/sometimes /often or always),
• Do you feel yourself depressed (seldom or never/sometimes /often or always).

Positive life orientation was regarded to be present if the participant answered "yes" or "seldom or never" to these six questions. These domains have been suggested to be major components of psychological well-being among older people. [8 303] This questionnaire has been used in a previous study, where positive life orientation was shown to predict mortality in older people. [293] These questions have also been

shown to have good concurrent validity with the RAND-36 questionnaire. [304]

The participants were also asked to rate their whole life course (life experiences, fullness of life, ingredients) using the Finnish school marks from 4 (worst) to 10 (best). Visual analogue scales (VAS; 10 cm) were used to assess present global happiness (0=very unhappy, 10=very happy).

Negative affect was further assessed with the Zung self-rating depression scale[19], a widely used instrument in epidemiological studies, embedded in the questionnaire. It consists of 20 items which were coded into a score as instructed. A person with a Zung score below 50 points was considered normal, with a score of 50-59 was considered to suffer from mild depression and a score of 60-69 was considered to suffer from moderate to marked depression.

9.8 MORTALITY FOLLOW-UP

Total mortality of the study population was retrieved from the National Population Information System of the Finnish Population Register Centre, which keeps registry of all Finnish citizens through 2000 and up to 31 December 2002. According to the Centre, assessment of vital status is very reliable for people having their permanent place of residence in Finland (over 95% of the present cohort in 2000) irrespective whether they die in Finland or abroad. Also, the assessment of the vital status for the Finnish citizens living permanently abroad is quite reliable.

9.9 ETHICAL CONSIDERATIONS

The follow-up study has been approved by the Ethical Committee of the Department of Medicine of the Helsinki University Hospital.

9.10 STATISTICAL METHODS

NCSS software was used for the analyses (NCSS Statistical Software, Kaysville, UT; Internet: www.ncss.com). In statistical analyses two-tailed tests were used and P values < 0.05 were considered as significant. Descriptive statistics, T-tests, nonparametric tests, and analyses of covariance (ANCOVA) were used to compare continuous variables. Chi-square and trend tests were used to compare proportions, and Spearman rank coefficients to assess correlations. Differences in survival were analyzed using Kaplan-Meier curves and log-rank tests. Relative risks (RR) with their 95% confidence intervals (CI) for mortality were calculated using Cox's

proportional hazards regression. The assumptions for proportional hazards were tested where appropriate. Other risk factors were adjusted for in respective models. The eight RAND-36 scales were constructed as instructed. [40] The physical component summary (PCS) and the mental component summary (MCS) scores were calculated of the eight RAND-36 scales as instructed. [45]

9.11 THE CHARACTERISTICS OF INDIVIDUAL RISK FACTORS DURING FOLLOW-UP

Due to missing data, the number of participants in the substudy analysis for different risk factors varies. Besides, there were some differences in the baseline variables and protocol of each substudy. These characteristics are outlined in Table 7.

Table 7. The number of men for whom risk factor data were available at baseline and during follow-up in each substudy. The number of men in the original cohort in 1964-1973 is 3.490 men. The numbers during follow-up differ due to missing data and differences in substudy protocols, as described in Data and methods. The Roman numbers refer to the respective original publication.

	I Weight gain	II Cholesterol	III Alcohol	IV Smoking	V & VI Risk factor clustering
1964-1973		3.277			
1974	1.657	2.245	1.808	1.658	1.203
1980			1.654		
1985-6	1.275	1.246	1.275		
2000 RAND-36 questionnaire	1.147	1.820	1.216	1.131	855 (V)
2002-3 Questionnaire of well-being					633 (VI)
Total follow-up, years	26	39	29	26	26-28

9.11.1 STUDY I: WEIGHT GAIN

For this substudy, the impact of weight gain on mortality and HRQoL was examined in 2.206 men, who in 1974 recalled their weight at 25 years of age. In closer examinations, 549 were found to have a history or signs of chronic diseases or medication and were excluded from the analyses. In 1974 weight and height were measured and the BMI was calculated. The change in body weight during early midlife was calculated as weight in 1974 (average age 47 years) minus weight at the age of 25. According to this change in body weight the men were then categorized into quartiles as outlined in Table 8. The quartiles were used in the further analyses of the effects of weight change. Because weight loss may indicate subclinical disease, the lowest quartile was further divided into those who did not gain weight and those whose weight increased less than 4.1 kg, and thus the analyses include five weight change groups.

Table 8. Classification of the change of body weight from age 25 to 1974 in the study population (n=1.657). The lowest quartile is further divided into those who did not gain weight (1a) and those whose weight increased less than 4.1 kg (1b).

Quartile	Number of men	Change of body weight, kg
1a	188	Loss or no gain
1b	244	0.1 to 4.0
2	415	4.1 to 9.0
3	385	9.1 to 14.9
4	425	≥ 15.0

Data on weight are subsequently available at several time points. The weight of 1.275 men (82% of survivors) was later measured in 1986 when they were re-assessed also with questionnaires and laboratory examinations.

In 2000 the mailed survey was sent to survivors (n=1.265), self reported weight and responses for the RAND-36 questionnaire are available for 1.147 (90.7 %) men. The analysis was adjusted to covariates (age, smoking, alcohol consumption, subjective health and physical fitness in 1974, body weight at 25 years and at year 2000) which were not considered to be in the pathogenetic pathway between weight gain and clinical end points. The total mean follow-up time is 26 years.

9.11.2 STUDY II: CHOLESTEROL

This substudy on the associations of cholesterol, mortality and HRQoL includes the 3.277 men (94 % of the total cohort) for whom baseline serum cholesterol measurements were available in 1964-1973. Follow-up examinations were made in 1974, 1985-6 and 2000. Total follow-up time is up to 39 years. The follow-up data are comprehensive at baseline and at the end, whereas the three in-between evaluations include only part of the study population. During follow-up, fasting serum cholesterol was measured in 1974 in 2.245 men and in 1985-6 in 1.246 men. In 2000 cholesterol values were based on self-report by 1.292 (71%) men.

For the measurements in 1964-73 and 1974, serum cholesterol concentration was determined using the method of Huang et al.[305] Since then routine laboratory analyses were performed using enzymatic methods, which yield lower values. Hence, corrected values have been used for the present analyses; the conclusions nevertheless remained the same when original values were used. For the survival analyses the results are presented in two fashions:

1) According to the baseline cholesterol values divided into per 1 mmol/L increasing groups as follows:
   - ≤5.0 mmol/L (n = 224),
   - 5.1 to 6.0 mmol/L (n = 803),
   - 6.1 to 7.0 mmol/L (n = 1.170),
   - 7.1 to 8.0 mmol/L (n = 720),
   - 8.1 to 9.0 mmol/L (n = 255),
   - and >9.0 mmol/L (n = 105),
2) Comparing the lowest cholesterol group (≤5.0 mmol/L, n =224) with other groups combined.

This second method was used for the HRQoL analyses. The RAND-36 scores were available for 1.820 of the 2.251 surviving men (80.9%) in 2000.

9.11.3 STUDY III: ALCOHOL

The impact of alcohol consumption in midlife in 1974 on mortality and HRQoL in old age in 2000 was analyzed for this study. The total mean follow-up time is 29 years. At baseline in 1974 detailed alcohol consumption data was collected with a questionnaire for 1.808 men, when they were asked to report their weekly alcohol consumption (beer, wine, and liquor separately) during the past year. One unit of alcohol (”a restaurant unit”: a bottle of beer, a glass of wine, a single drink of spirits) was calculated to contain 14 grams of pure alcohol. The alcohol intake was summed up to produce an approximation of total consumption as grams of ethanol consumed per week. The consumption at baseline (grams/week) was divided in three categories:

1) zero consumption (n=116)
2 moderate consumption (1 to 349 g of pure alcohol per week, mean consumption less than 3 drinks/day, n=1.519)
3) high consumption (350 g/week or more, mean consumption 5 drinks/day, n=173)

Of the initial 1.808 men, 1.654 men were re-examined in 1980, and 1.275 (82% of survivors) could be re-assessed in 1985-86 with questionnaires and laboratory examinations. This survey included the same question about alcohol consumption as at baseline. Serum gamma-glutamyl transferase activity was measured in 235 men and this information was used to validate the reported alcohol consumption.

In 2000, 1.216 (86%) of 1.416 surviving participants responded to the mailed questionnaire and the RAND-36 scores were calculated. The question on alcohol consumption in the 2000 survey was similar to the earlier surveys of 1974 and 1986. Baseline alcohol consumption was not different between respondents and non-respondents.

9.11.4 STUDY IV: SMOKING

For this study the impact of smoking status in 1974 on mortality and HRQoL in 2000 was analyzed, with a mean follow-up time of 26 years. Smoking status was collected with a questionnaire for 2.464 men at baseline in 1974. The 581 men who had any chronic disease or medication were excluded from the analysis, as well as those 160 men who reported smoking cigars or pipe. The smoking status was not available for 5 men. The 1.658 men in the substudy cohort were classified into four groups according to their reported smoking status in 1974:

1) never-smokers (n=614), men who had never smoked and were not currently smoking,
2) ex-smokers (n=650), those who had been smokers before, but had quitted smoking by 1974,
3) 1-10 cigarettes /day (n=87), those who were smoking 1-10 cigarettes daily,
4) 11-20 cigarettes/day (n=119),
5) over 20 cigarettes /day (n=188).

The duration of the smoking habit or the length of cessation of smoking before 1974 was not recorded.

In 2000, the smoking status and RAND-36 scores were assessed in 1.131 men (88, 0%) of the total cohort of 1.286 men alive.

9.11.5 STUDY V: CARDIOVASCULAR RISK PROFILE

For this substudy the relationship between total cardiovascular risk in midlife and HRQoL and mortality in old age was examined by comparing men with a low risk factor status with men with risk factor clustering at baseline. From the original cohort of 3.490 participants, the men who had any chronic disease or medication were excluded, and among the healthy participants, two groups of 593 men with low and 610 men with high levels of risk factors were identified in 1974. Both groups acted as the usual care groups in the multifactorial intervention trial described above. [299]

In order to be rated at high risk, at least one of the six risk factors listed in Table 9 had to be present on two occasions (except elevated one-hour glucose only once) at baseline; otherwise, the classification was low risk.

Table 9. The levels of the predefined risk factors that were employed to identify the 610 men in the high risk group in the subcohort of 1.222 healthy men in 1974.

• Relative body weight ≥ 120%, corresponding to BMI of 27.8 kg/m^2
• Smoking > 10 cigarettes/day
• Systolic and diastolic blood pressure ≥160/95 mm Hg
• Serum cholesterol ≥7.0 mmol/L
• Serum triglycerides ≥1.7 mmol/L
• One-hour post-load glucose value ≥ 9.0 mmol/L.

All the men in the high-risk group attended a check-up on two occasions, but those men with none of the risk factors on the first occasion did not necessarily proceed to second measurements. The exact proportion of these men is not available in the present database. The average number of risk factors in the high-risk group was 2.1.

In the 2000 query responses including the RAND-36 questionnaire were gathered from 448 participants in the baseline low-risk group and from 407 in the high-risk group of the total cohort of men alive. Response rates were 90.7% and 88.5%, respectively. Total time of follow-up was 26 years.

9.11.6 STUDY VI: PSYCHOLOGICAL WELL-BEING

The data of the two groups of healthy men (593 men with low and 610 men with high levels of predefined risk factors), which were identified in 1974 and employed for substudy V, were also used for this substudy examining the impact of midlife cardiovascular risk factors on psychological well being in old age. For this substudy, mortality was available through December 31st 2002. In 2002-2003 a questionnaire was sent to all survivors. Depression was evaluated with the Zung self-rating depression scale [19] and positive affect was assessed with the six self rated questions as described in detail above. The response rate was 74% (n=336) and 71% (n=297) in the low and high risk groups, respectively (P=0.4).The average age of responders was 76 years.

10 RESULTS

10.2 WEIGHT GAIN

10.1.1 BASELINE CHARACTERISTICS

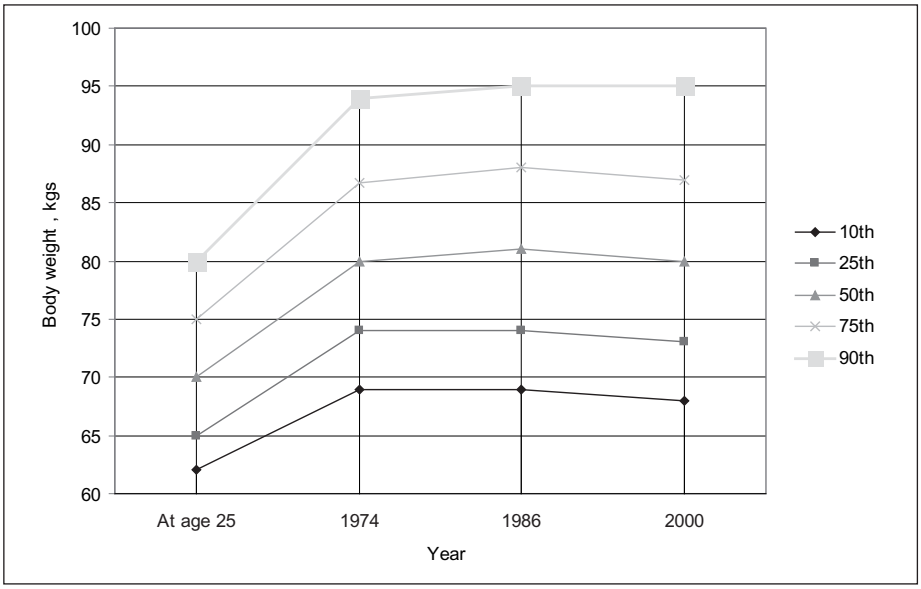
For substudy I, the effect of weight gain on mortality and HRQoL was examined in 1.657 men.

At baseline in 1974, the mean age of the cohort was 47 years, SD 4 years. The mean BMI at the age of 25 was 22.7 kg/m^2 and 25.8 kg/m^2 in 1974, denoting an increase from the mean weight of 71.2 to 81.0 kgs. 14.7 % were smokers. Mean alcohol consumption was 121.9 g/week.

10.1.2 THE DEVELOPMENT OF WEIGHT OVER THE STUDY PERIOD

Lifetime changes in body weight are shown in Figure 2.

Figure 2. Distribution and change of body weight (kg) during the follow-up.

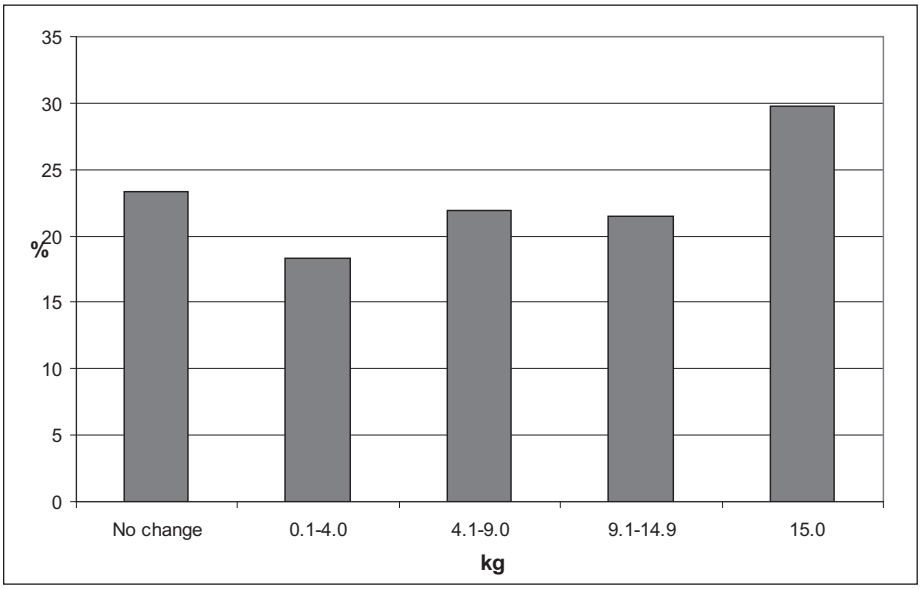


Weight increased from 25 years of age until midlife, but not thereafter. Less than 1% (n=11) of this cohort had BMI > 30 kg/m2 at 25 years, compared to 7.2% (n=120) in 1974. Mean BMIs (SD) were 22.7 kg/m^2 (SD 2.1), 25.8 kg/m^2 (2.7), 26.1 kg/m2 (3.0), and 25.8 kg/m^2 (3.1), at 25 years, 1974, 1986 and 2000, respectively. Mean weight gain from the age of 25 years until 1974 was 9.8 kg (SD 8.3) and the gain was significantly inversely correlated with weight at 25 years (r= -0.305, P<0.0001).

10.1.3 MORTALITY DURING FOLLOW-UP

The average age among survivors in this substudy was 73 years (SD 4). Through December 31, 2000, 392 (23.5%) men had died. Weight at 25 years of age did not predict mortality. Mortality was similar in the lower weight gain groups, but was significantly higher (29.8%) in the highest quartile of weight gain of ≥15.0 kg. There was no significant over-mortality (23.3%) among those who did not report weight gain during midlife. (Figure 2.)

Figure 3. Mortality (%) according to the weight gain from 25 years of age until 1974, when the mean age was 47 years.

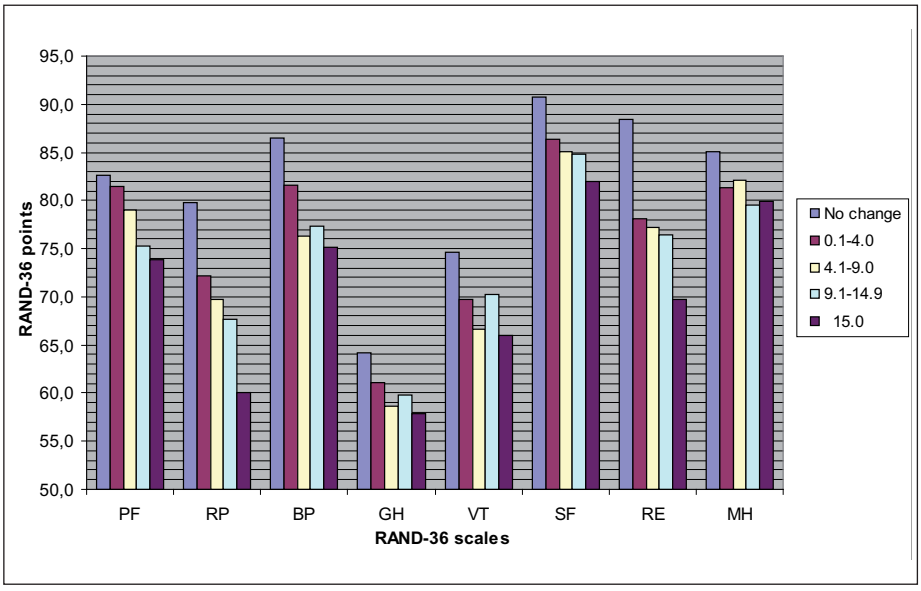


The relationship between mortality and weight gain was further analyzed adjusted for age, body weight at 25 years, smoking, alcohol consumption, subjective health and physical fitness in 1974. The highest quartile of weight gain was associated with 39% increased total mortality vs. lower quartiles (OR 1.39, 95% CI 1.12 to 1.73) in these analyzes.

10.1.4 HEALTH-RELATED QUALITY OF LIFE IN 2000

In the 2000 survey, scores for the RAND-36 scales did not significantly differentiate for the quartiles of body weight at age 25. According to weight quartiles in 2000, significant and inverse patterns with increasing weight were observed in the scores of Physical functioning, Role limitations due to physical problems and Role limitations due to mental problems. The differences seen in other scales of RAND-36 were not statistically significant. In contrast, there were clear differences in all the scales according to the quartiles of midlife weight gain (Figure 4.), when the scales were adjusted for age, weight at age 25 and in 2000, smoking and alcohol consumption, subjective health and physical fitness in 1974. In seven out the eight RAND-36 scales the differences were statistically significant between the weight gain groups. Men with no weight gain in midlife had consistently the best quality of life.

Figure 4. Weight gain (kgs) in midlife and quality of life (RAND-36) in old age in 2000



Abbreviations (and global P values) for the individual scales: PF= Physical functioning (P=0.002), RP= Role limitations due to physical problems (P=0.008), BP= Bodily pain (P<0.001) , GH =

General health (P=0.02), VT= Energy/vitality (P<0.001), SF= Social functioning (P=0.02), RE= Role limitations due to problems of mental health (P=0.006), MH= Mental health/emotional well-being (P=0.06).
In all scales the scores were adjusted for age, smoking, alcohol consumption, subjective health and physical fitness in 1974, and body weight at age 25 and in 2000.

10.2 CHOLESTEROL

10.2.1 BASELINE CHARACTERISTICS

At baseline of this substudy, the average age of the cohort (n=3.277) was 38 years (SD 4). 224 men (6.8% of all) had serum cholesterol values of 5.0 mmol/L or lower. Nearly half of the men (44.9%) were smokers.

In 1974, the distributions of subjective health and physical fitness did not differ between the low cholesterol group and other groups combined: the P-values for the overall differences between the groups were 0.37 (subjective health) and 0.75 (physical fitness). Only 6.3% and 6.6% of the men in the lowest cholesterol group and others, respectively, reported their subjective health as “poor” or “very poor”. The respective proportions for physical fitness were 14.9% and 16.2%.

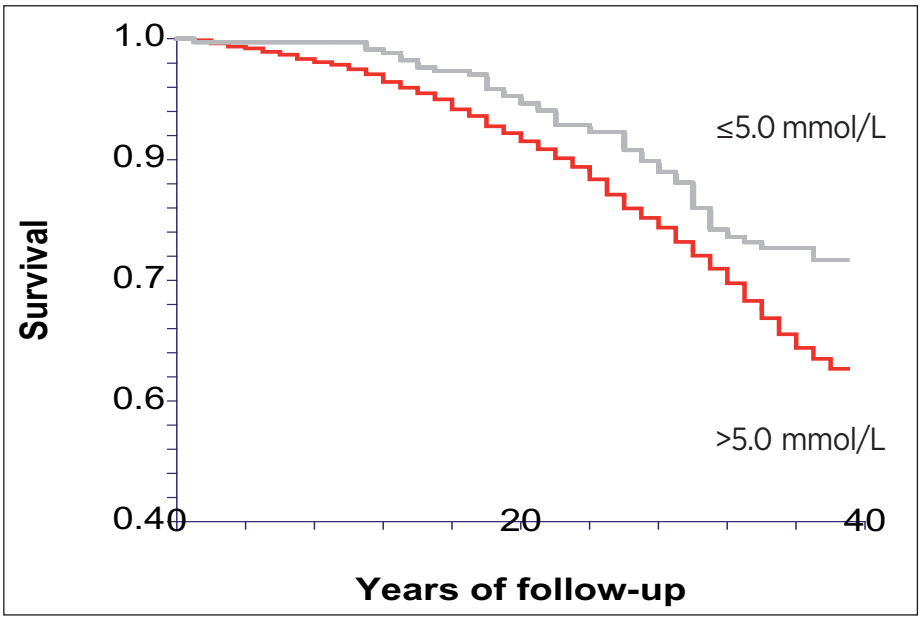
10.2.2 THE DEVELOPMENT OF CHOLESTEROL LEVELS OVER THE STUDY PERIOD

Cholesterol values tracked quite well during the long follow-up. Those alive in 2000 (n=1.292) reported their latest serum cholesterol value in the 2000 survey showing that baseline differences of cholesterol values had basically stayed the same over the years, with a general regression to the mean, except in the lowest cholesterol group, where there was no apparent change from baseline. 16% of responders reported using cholesterol lowering medication in 2000.

10.2.3 MORTALITY DURING FOLLOW-UP

After a follow-up period of 39 years, 1.173 deaths (35.8% of all) from all causes occurred. Total 39-year mortality increased in a graded manner according to the baseline serum cholesterol level (Table 10.). Survival curves of the lowest cholesterol group (≤5.0 mmol/L) vs. other groups combined are shown in Figure 5.

Figure 5. Survival curves of lowest baseline cholesterol group (≤5.0 mmol/L, n=224) vs. higher cholesterol group (>5.0 mmol/L, n=3.053). P-values between groups were determined with log rank tests. (P= 0.003)



The curves demonstrate that the survival benefit in the lowest cholesterol group was even accentuated during the last years of the follow-up.

As indicated in Table 10, multivariate analyses showed that the relative hazard of death rose by 11% (95% CI 6% to 17%) for every increase of 1 mmol/L of cholesterol (adjusted for age, body mass index and the year of first cholesterol measurement). The relative hazard was insensitive to more baseline risk factors in the model.

Table 10. Multivariate relative risk (RR) of 39-year mortality according to baseline cholesterol in the total cohort (n=3.277)

Baseline cholesterol	Risk ratio of mortality*		
	Model A	Model B	Model C
Continuous variable, per 1 mmol/L	1.11 (1.05-1.16) P<0.0001	1.11 (1.06-1.17) P<0.0001	1.09 (1.04-1.15) P=0.001
≤ 5.0 mmol/L (n=224) compared to > 5.0mmol/L (n= 3.053)	0.76 (0.59-1.00) P=0.05	0.75 (0.57- 0.98) P=0.04	0.72 (0.53-0.97) P=0.04

**Risk ratio calculated using the Cox proportional hazards model (with 95 % CI)*

Model A: adjusted for age

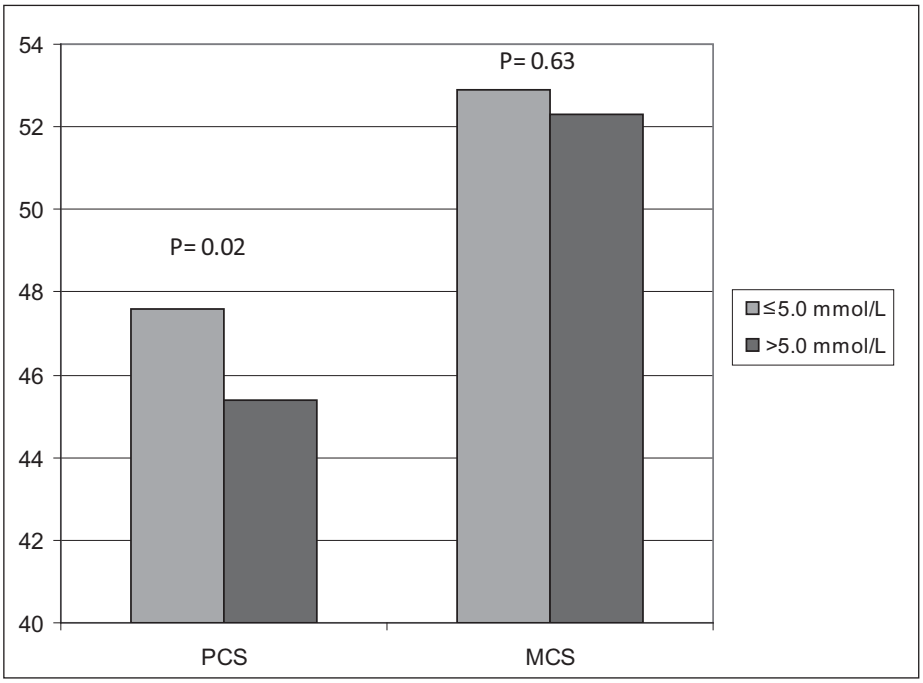
Model B: adjusted for age, BMI, and the year of first cholesterol measurement

Model C: adjusted for age, BMI, smoking, systolic blood pressure, one-hour glucose (log transformed), and the year of first cholesterol measurement

10.2.4 HEALTH-RELATED QUALITY OF LIFE IN 2000

The response rate to the 2000 survey was 81% (n=1.820). Average age of respondents was 73 years (SD 4). Age and baseline cholesterol concentrations were identical in respondents and non-respondents. The Physical component summary score PCS (adjusted for blood pressure, BMI, baseline smoking, and age) showed a markedly better physical quality of life score in the group with the lowest baseline cholesterol level (≤5.0 mmol/L, n=224) compared with the combined higher-cholesterol group (>5.0 mmol/L, n=3.053): 47.6 points versus 45.4 points (P = 0.02) (Figure 6). Of the individual RAND-36 scales, Physical functioning and Bodily pain were significantly better by 7.8 and 6.4 points, respectively, for the lowest baseline cholesterol group (Figure 7). The differences between the RAND-36 scales denoting mental heath were not statistically significant, and there was no difference in the mental component score MCS between the low-cholesterol and combined higher cholesterol groups (52.9 versus 52.3 points, P=0.63).

Figure 6. Baseline cholesterol and physical (PCS) and mental (MCS) quality of life in old age in 2000.



The Physical component summary (PCS) and Mental component summary (MCS) scores in 2000 according to the baseline serum cholesterol levels (≥5.0 mmol/L vs. <5.0 mmol/L) measured in 1964-1973. PCS and MCS were calculated using the RAND-36 scales. Adjusted for age, systolic blood pressure, BMI and baseline smoking.

Figure 7. Baseline cholesterol and health-related quality of life (RAND-36) in old age in 2000.

Baseline cholesterol and health-related quality of life (RAND-36) in old age in 2000. In all RAND-36 scales a score of 100 is the best possible. Abbreviations (and P-values) for the RAND-36 scales: PF = Physical functioning (P=<0.001), RP = Role limitations due to physical health (P=0.34) , BP= Bodily pain (P=0.03), GH= General health (P=0.08), VT= Energy/vitality (P=0.49), SF= Social functioning (P=0.13), RE= Role limitations due to mental problems (P=0.36), MH= Mental health/emotional well-being (P=0.86). In all scales the scores were adjusted for age, baseline systolic blood pressure and BMI.

10.2 ALCOHOL

10.3.1 BASELINE

Among the 1.808 participants in this substudy, reported mean alcohol consumption in 1974 was 159 g/week (SD 153, median 123 g/week, interquartile range 56 to 238). Several cardiovascular risk factors measured in 1974 became progressively more prevalent with increasing alcohol consumption (0, 1 to 349, and ≥350 grams/ week). Also reported weight gain from the age 25 years was positively associated with the alcohol consumption in 1974. Self-report of subjective health and physical

fitness in the three groups in 1974 showed that higher alcohol consumption was associated with worse profiles.

10.3.2 THE DEVELOPMENT OF ALCOHOL CONSUMPTION DURING FOLLOW-UP

Age-adjusted alcohol consumption during the 29-year follow-up in those survivors who reported their current consumption in 2000 (n=960) was relatively stable in lower categories, but decreased markedly in the highest category.

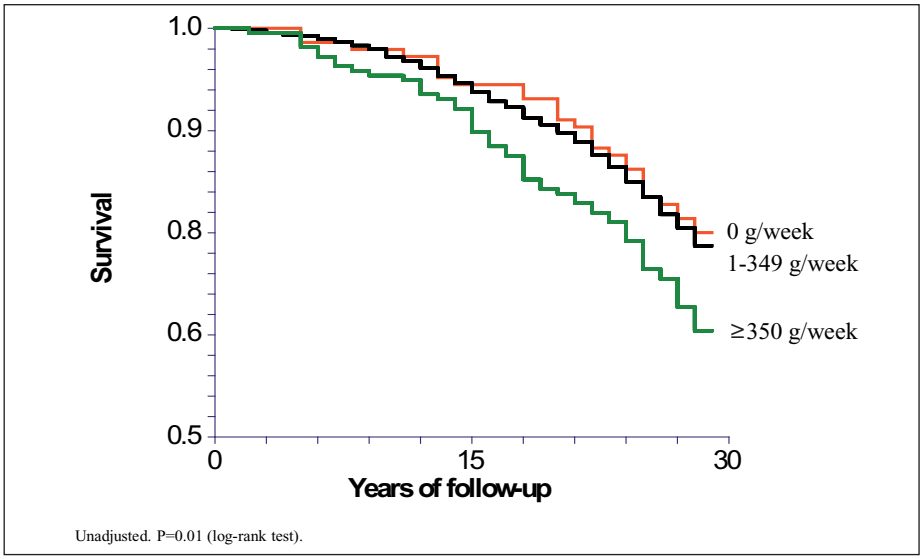
In the 2000 survey (n=1.215), reported mean consumption was 117 g/week (SD 137, median 70 g/week, interquartile range 28 to 154). Alcohol consumptions in 1974 and 2000 were significantly correlated (r=0.53, P<0.0001).

In 1986, serum gamma GT activity measured in 235 men was significantly correlated with the reported alcohol consumption (r= 0.41, P<0.0001).

10.3.3 MORTALITY DURING FOLLOW-UP

During the 29-year follow-up, 499 men (27.6% of the initial 1974 cohort) died. Crude mortalities in the three groups were significantly different, survival curves are shown in Figure 6. Mortality was significantly higher in the highest baseline category of reported alcohol consumption (37.6%), but fairly comparable in other groups (25.0% and 26.7% in abstainers and moderate drinkers, respectively).

Fig.6. Survival curves of the baseline alcohol consumption groups.



The proportion of cardiovascular deaths (determined up to 1999) of all deaths was 37.7% in the cohort, no significant differences were observed between the three alcohol consumption groups (P=0.5). Because alcohol consumption ≥350 grams/week was associated with higher levels of risk factors at baseline, multivariate analyses using proportional hazards regression were also performed. In these analyses, zero and high alcohol consumption were compared with moderate intake (Table 11). When important risk factors (age, smoking, serum cholesterol and 1-hour post-load glucose) were added to the model, alcohol consumption was no longer a significant predictor of mortality.

Table 11. Proportional hazards analysis of 29-year mortality in study groups.

Alcohol consumption group (grams/week) in 1974	Model A	Model B*	Model C*
0, n=116	0.93 (0.64-1.35)	0.95 (0.65-1.38)	0.99 (0.68-1.45)
1-349, n=1.519 (reference group)	1.0	1.0	1.0
>349, n=173	1.50 (1.14-1.94)	1.34 (1.03-1.74)	1.26 (0.96-1.65)

Model A: No adjustments

Model B: Adjusted for age and smoking

Model C: Adjusted for age, smoking, serum cholesterol and one-hour post-load glucose

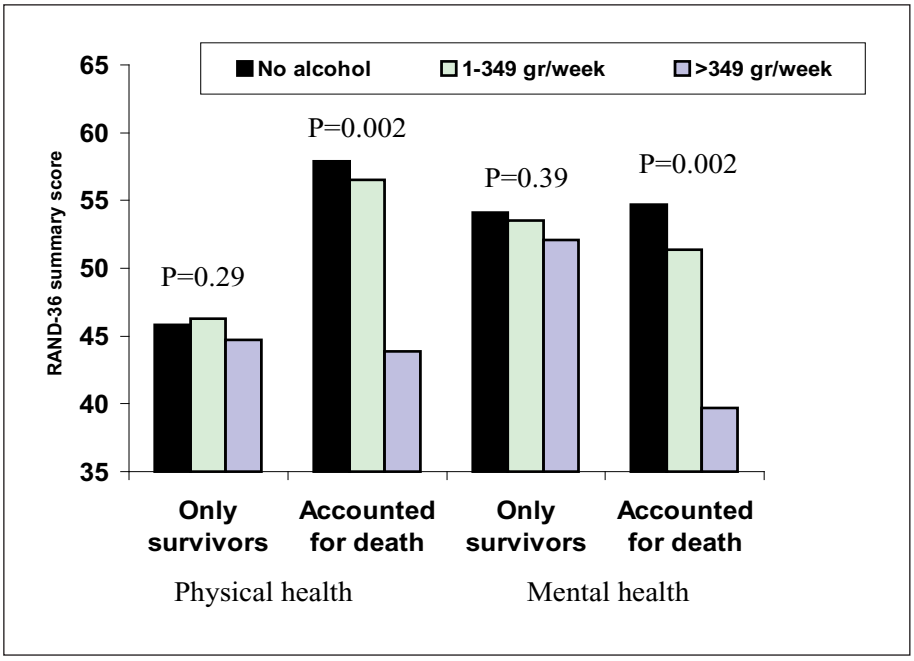
**Covariates simultaneously in the model*

10.3.4 HEALTH-RELATED QUALITY OF LIFE IN 2000

In 2000, 87% (n=1.216) of the survivors responded to the questionnaire survey. Non-respondents (n=200) had a higher mean baseline alcohol consumption than respondents (181 g/week vs. 148 g/week, P=0.01). This was due to a greater proportion of high alcohol consumption among non-respondents (12.7% vs. 8.1%), while proportions of abstainers were the same (6.6%). In 2000, over 90% were retired but 97-99% were home dwelling without significant differences between the three groups. Risk factor differences between the groups had diminished among respondents, but there were still significantly more smokers (P=0.001) and significantly less regular exercise (P=0.03) among the high alcohol consumption group. Prevalences of reported diseases were not significantly different between the groups.

Health-related quality of life was assessed with the RAND-36 questionnaire in 2000. There were no significant differences in the component summary scores PCS or MCS between the alcohol consumption groups (Figure 8, adjusted for age). The results were essentially similar when the data were further adjusted for smoking, systolic blood pressure, serum cholesterol and BMI. However, significant differences were seen when the quality of life was further accounted for deaths during follow-up. When adjusted for age, both physical and mental health were clearly poorer in men with the highest alcohol consumption, but fairly similar between zero and moderate consumption (Figure 8).

Figure 8. Baseline alcohol consumption in 1974and health-related quality of life in 2000 as measured by RAND-36 component summary scores PCS and MCS for physical and mental quality of life, respectively.



The original PCS and MCS scores were calculated using the RAND-36 scales. Based on the original score, the new values of physical health and mental health ("Accounted for death") estimate the proportion (in percentage) of participants who are likely to be healthy 1 year later. The transformed values include deaths during the follow-up as described in the Methods section. P-values indicate difference between the alcohol consumption groups. Adjusted for age.

10.4 SMOKING

10.4.1 BASELINE CHARACTERISTICS

Of the 1.658 men, 614 (37.0%) were never-smokers at baseline in 1974. 650 men (39.2%) had quitted smoking earlier. The number of cigarette smokers in the different groups according to the number of cigarettes smoked were 87 (5.3% of the total cohort), 119 (7.2%) and 188 (11.3%) in the groups of 1-10 cigarettes, 11-20 cigarettes and more than 20 cigarettes daily, respectively.

At baseline there were significant differences in age, BMI, weight gain from age 25 to baseline, BP, cholesterol, triglycerides, one-hour post-load glucose, reported alcohol consumption and self-perceived health between the groups.

10.4.2 CHANGES IN SMOKING BEHAVIOR OVER THE STUDY PERIOD

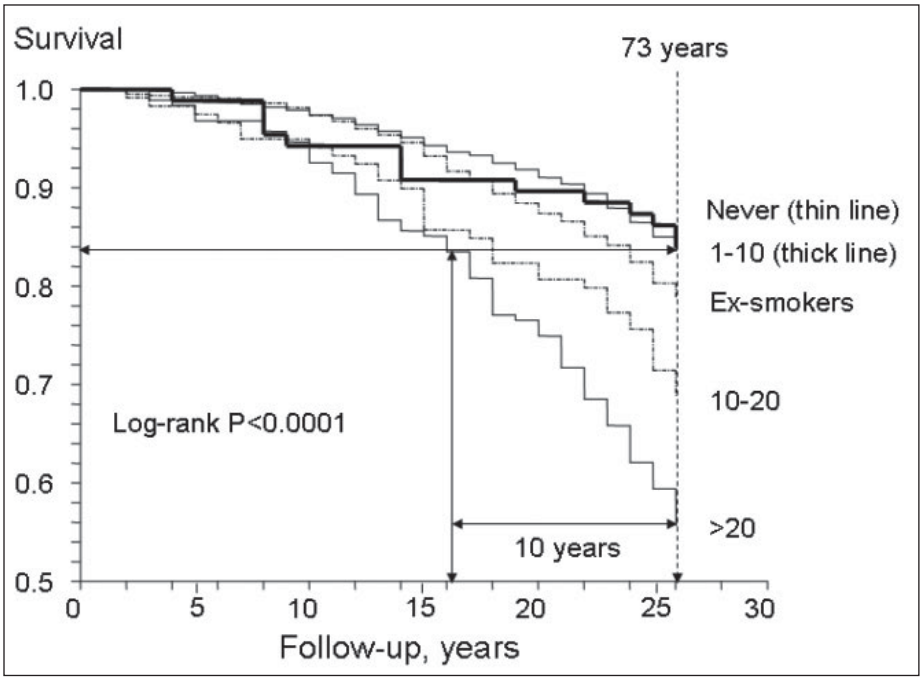
In 2000 the current smoking status was gathered from 1.131 men. The median age of responders was 73 years (interquartile range 70 to 76 years). Mean response rate was 87.9 %.

The cessation rate among smokers was large during the follow-up: from 69% of those smoking over 20 cigarettes to 82% in the group smoking 1-10 cigarettes daily at baseline. Thus, in the 2000 query, only 6.9% (n= 78) of the respondents were currently smoking.

10.4.3 MORTALITY DURING FOLLOW-UP ACCORDING TO SMOKING STATUS IN 1974

During the 26-year follow up 372 men (22.4%) died. Figure 9. shows the association between the smoking status in 1974 and mortality by the year 2000. The amount of daily cigarettes predicted mortality in a graded manner ($P<0.0001$). Although two out of three (69%) had stopped smoking since baseline, only 56% of those smoking over 20 cigarettes a day at the mean age of 48 were alive at the mean age of 73, as compared to 84% of never-smokers.

Figure 9. The association of smoking status and the number of cigarettes smoked daily at baseline in 1974 and mortality during the 26- year follow-up.



Arrows indicate the difference of survival in years between never-smokers and smokers of more than 20 cigarettes daily. Dotted line indicates survival to the mean age of 73 years.

Using the never-smokers as the referent group, Table 12 shows the risk of total mortality after adjustment for age only and further for age, baseline cardiovascular risk factors (BMI, cholesterol, SBP and 1-hour post-load glucose) and alcohol consumption. In the latter analysis the men smoking over 20 cigarettes daily at baseline had a total mortality risk that was over 2.5 fold of that of never-smokers.

Table 12. Relative risk for total mortality during the 26 years of follow-up according to smoking status at baseline in 1974. Never-smokers as referent.

Smoking status in 1974	Model 1 *		Model 2 †	
	RR	95% CI	RR	95% CI
Ex-smokers	1.21	0.93, 1.57	1.05	0.80, 1.37
1-10 cigarettes/day	0.95	0.54, 1.66	0.82	0.46, 1.47
11-20 cigarettes/day	2.01	1.38, 2.93	1.60	1.08, 2.37
> 20 cigarettes/day	3.14	2.35, 4.20	2.61	1.92, 3.54

** Adjusted for age.*

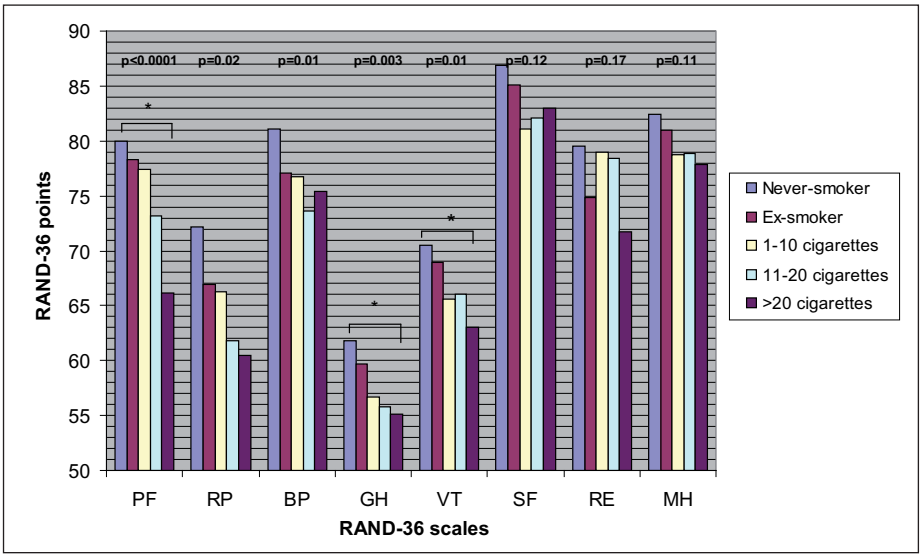
† Adjusted for age, alcohol consumption, BMI, cholesterol, SBP and 1-hour post-load glucose at baseline.

RR: relative risk; 95% CI: 95% confidence interval, BMI: Body Mass Index, SBP: systolic blood pressure

10.4.4 HEALTH-RELATED QUALITY OF LIFE IN 2000

The association between smoking status in 1974 and age-adjusted HRQoL in 2000 is illustrated as RAND-36 scales in Figure 10.

Figure 10. The association of smoking status at baseline in 1974 and HRQoL as RAND-36 scores in 2000.



Abbreviations for the RAND-36 scales: PF = Physical functioning, RP = Role limitations due to physical health, BP= Bodily pain, GH= General health, VT= Energy/vitality, SF= Social functioning, RE= Role limitations due to mental problems, MH= Mental health/emotional well-being. Adjusted for age. P-values above bars depict the overall difference between groups.
(*) denote statistical significance seen in PF, GH, and VT between never-smokers and men smoking >20 cigarettes, using Bonferroni's correction for multiple comparisons.

The never-smokers had the highest (best) scores in all eight of the RAND-36 scales, although the differences were not statistically significant for the scales expressing the mental and social aspects of the quality of life (Social functioning, Role limitations due to mental problems, Mental health). Compared to smokers, especially large differences were seen in the scales of Physical functioning and Role limitations due to physical health, where never-smokers gained 13.7 and 11.7 higher points, denoting a decline of 17 and 16 per cent, respectively, for those smoking over 20 cigarettes a day (Figure 10). Compared to heavy smokers, the never-smokers in the cohort lived 10 years longer (Figure 9). Meanwhile, the difference in their level of disability, as suggested by the 13.7 point difference in the Physical functioning score, was equal to an age-difference of 10 years when compared to the age- and sex-matched general Finnish population norms. [40]

As in mortality, those who had quitted smoking before baseline examinations in 1974 did not generally seem to reach the RAND-36 points of never-smokers during the 26 year follow-up.

10.5 CARDIOVASCULAR RISK PROFILE

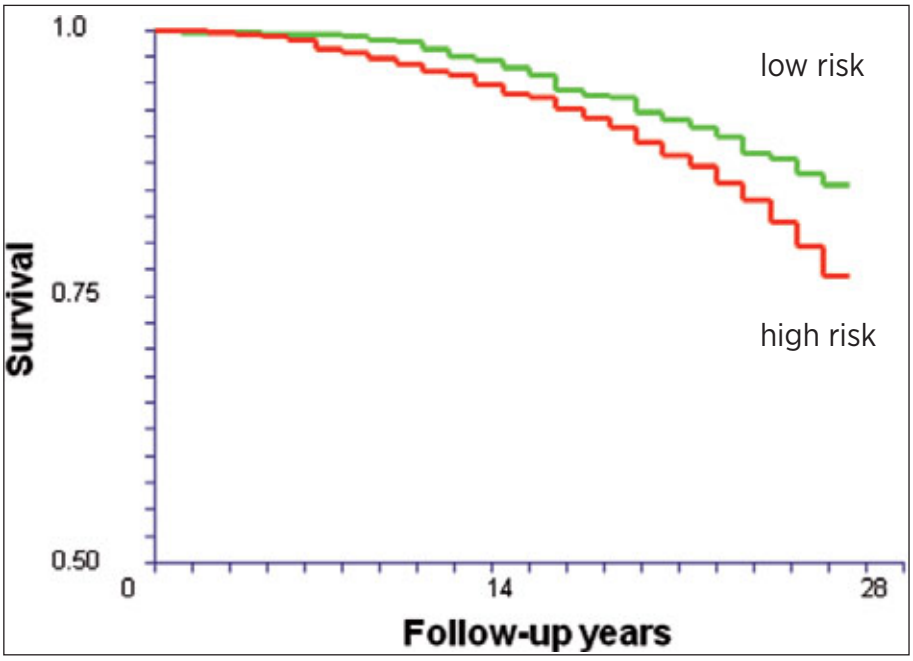
10.5.1 BASELINE CHARACTERISTICS IN 1974

For the substudy V, the mortality and old age quality of life of 593 men with low cardiovascular risk profiles in midlife were compared to 610 men with high risk profiles in midlife during a follow-up period of 26 years. All risk factor levels measured in 1974, and reported BMI at age 25 for the two groups were significantly lower at baseline in the low-risk group. Self-rated physical condition in 1974 was clearly better in the low-risk group ($P<0.0001$), whereas differences in self-rated general health were smaller, although statistically significant ($P=0.03$). In 1974, the proportion of men reporting their general health as "poor" or "very poor" was 3.1% and 4.1% in the low-risk and high-risk groups, respectively ($P=0.36$).

10.5.2 MORTALITY OVER THE STUDY PERIOD

Mortality data was gathered up to December 31, 2002. By this time altogether 303 (25%) men had died, 127 (21%) in the low-risk group and 176 (29%) in the high-risk group. (Figure 11.) The 29-year follow-up mortality was thus 54% higher (HR 1.54, 95% CI 1.19-2.00) in the high-risk group. When adjusted for age, weight at age 25 years and subjective health in 1974, the high-risk profile in middle age prevailed as an independent predictor of mortality (HR 1.42, 95% CI 1.11-1.81).

Figure 11. Survival curves of the baseline low and high cardiovascular risk



Unadjusted. P=0.001 (log-rank test).

10.5.3 HEALTH-RELATED QUALITY OF LIFE IN 2000

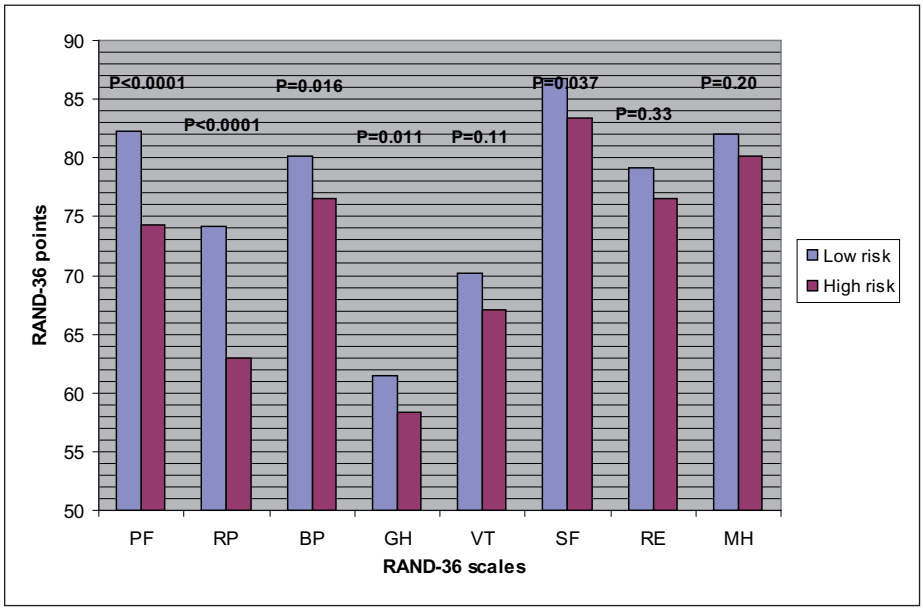
For the 2000 survey, the average age among survivors was 73 years (SD 4). The response rate was 90.7% for the low-risk and 88.5% for the high-risk group.

The men belonging to the high-risk group in 1974 reported a higher BMI, higher prevalence of smoking, and higher fasting blood glucose values in 2000 than the men in the low cardiovascular risk group. In contrast, differences in blood pressure and serum cholesterol had diminished, although men in the high risk group still reported more hypertension in 2000. They also reported a significantly more sedentary lifestyle and a higher prevalence of diabetes, congestive heart disease, pulmonary disease, and musculoskeletal disease.

The HRQoL of surviving participants was assessed with the RAND-36 instrument. In the low-risk group, all eight scales of RAND-36 indicated consistently better quality of life. Differences were statistically significant ($P<0.05$) for Physical function, Role physical, Bodily pain, General health and Social functioning (Figure 12.). The greatest differences of 8.0 and 11.2 points were seen in the scales denoting Physical

functioning and Role limitations due to physical problems, respectively, indicating a decline of 10 % and 15 % , respectively, for the group with high cardiovascular risk factor status at baseline. Of the two component summary scores only PCS, but not MCS was significantly different between the groups.

Figure 12. The age-adjusted association of risk status at baseline in 1974 and HRQoL as RAND-36 scores in 2000.



Abbreviations for the RAND-36 scales: PF = Physical functioning, RP = Role limitations due to physical health, BP= Bodily pain, GH= General health, VT= Energy/vitality, SF= Social functioning, RE= Role limitations due to mental problems, MH= Mental health/emotional well-being. P-values above bars depict the overall difference between the low risk and the high risk groups.

10.6 PSYCHOLOGICAL WELL-BEING

10.6.1 BASELINE CHARACTERISTICS IN 1974

The cohorts with low and high midlife risk status which were identified for substudy V were also used for this substudy examining the effect of midlife cardiovascular risk factors on the negative and positive affect in old age. 593 healthy men with low cardiovascular risk profiles in midlife were compared to 610 healthy men with high risk profiles in midlife. Thus the baseline data in 1974, as well as the RAND-36 scores are the same as displayed for substudy V. Mortality follow-up was through 2002.

10.6.2 PSYCHOLOGICAL WELL-BEING IN 2002-3

To evaluate psychological well-being, a questionnaire was sent to survivors (454 men in the low risk and 418 in the high risk group) in 2002-2003. 336 men in the low-risk group and 297 men in the high-risk group responded to this survey, giving response rates 74% and 71%, respectively. Non-respondents and respondents in 2002-3 had similar PCS scores in 2000, but scores for MCS tended to be lower among non-respondents. Of the respondents, 99% and 98% were home-dwelling, 94% and 97% were retired, and 85% and 90% were currently married in the low and high-risk groups, respectively. All these differences between groups were statistically non-significant. The data further emphasize the similar socioeconomic status of the two groups. Despite higher mortality in the high-risk group and selective survival, the gradient in risk factors between the groups had prevailed although they were somewhat reduced as compared to baseline.

Factors related to psychological well-being and attitudes towards life are shown in Table 6. The mental well-being of the low and high cardiovascular risk groups in 2002-3 is presented in Table 13.

Table 13. Variables of psychological well-being in 2003 in the low and high risk groups defined in 1974.

Factor	Low risk* n=336	High risk* n=297	P value
Satisfied with life, yes/no (%)	318/11 (96.7)	272/20 (93.2)	0.02
Feeling needed, yes/no (%)	118/210 (36.0)	92/198 (31.7)	0.13
Having plans for the future, yes/no (%)	222/98 (69.4)	185/105 (63.8)	0.07
Having zest for life, yes/no (%)	327/4 (98.8)	284/9 (96.9)	0.05
Feeling of depression, never or seldom/at times or often (%)	192/136 (58.5)	157/134 (54.0)	0.13
Feeling of loneliness, never or seldom/at times or often (%)	288/40 (87.8)	257/37 (87.4)	0.56
Positive life orientation, yes/no (%)	71/265 (21.1)	47/250 (15.8)	0.04
How do rate your life course on a scale from 4 =worst to 10 = best, mean (SE)	8.6 (0.04)	8.5 (0.04)	0.05
How do you rate your present happiness (0=very unhappy, 10=very happy), VAS mean (SE)	7.7 (0.09)	7.3 (0.09)	0.001
Zung score, points (SE)	34.3 (0.4)	36.0 (0.4)	0.007

Continuous variables (mean with SE) are adjusted for age.

** Percentages are calculated from the actual number of respondents.*

VAS= visual analogue scale (10 cm)

Although not all differences are statistically significant, the data are consistently better in the original low-risk group as compared to the high-risk group. Significant differences were seen in life satisfaction, feeling of happiness assessed with VAS, positive life orientation as a whole and the Zung depression score.

The difference in the feeling of happiness (VAS) was tested further with multivariate analysis. The difference between the low and high-risk group prevailed (P=0.01) after adjustment for age, years of education, self-rated health in 1974, alcohol consumption in 1974, and feeling of depression in 2002-3.

11 DISCUSSION

11.1 MAIN FINDINGS

With the increase in longevity also the prevalence of chronic diseases and subsequent disability and functional impairment among the population is expected to rise. Good quality of life during these additional years is thus essential both from the individual's and society's point of view. Person reported information on how individuals consider the impact of disability or illness on their functioning or well-being has become a vital addition to the global assessment of health. This has only recently become possible in a large scale following the introduction of questionnaires that are valid and reliable as well as easy to use.

The studies presented in this thesis investigated the impact of lifestyle and modifiable risk factors, which all affect cardiovascular health in the long term, on mortality and HRQoL. The hypothesis was that since much of the illness and disability in older people is related to cardiovascular risk factors in midlife, lower risk factor status not only postpones death, but also reduces disability and infirmity, which is then illustrated by better quality of life in old age.

Negative levels of all these risk factors examined: weight gain, alcohol, cholesterol and smoking individually, as well as in combination in midlife all led to diminished life expectancy, as could be anticipated in the light of previous studies. The novel finding in these studies is that in addition to a shorter life span, these risk factors are associated with significant reductions especially in the physical components of HRQoL, and in most cases, also in the social and mental domains of quality of life.

11.2 DATA AND METHODS

The especially long follow-up time of the study cohort presents a distinctive approach to observe subsequent health consequences of different cardiovascular risk factors in midlife. The results are based on a large cohort of men who were all healthy without any chronic diseases or medication at baseline. The cohort is quite homogenous: All the men were from higher socioeconomic strata with similar job status mostly belonging to the professional executive grade. This is an asset in evaluating quality of life because social class has an apparent impact on morbidity and mortality. [306] The availability of data on several risk factors at baseline has made it possible to perform extensive multivariate adjustments for potential confounding factors. Mortality

follow-up with national registers was reliable and 100% complete, and during the follow-up of up to 39 years there were a substantial number of mortality endpoints. HRQoL was measured with a widely used and validated instrument (RAND-36) with a good overall response-rate, ranging from 71% to 91 % in the substudies.

11.3 WEIGHT GAIN

This substudy examined the effect of weight change from the age of 25 to the average age of 47 on mortality and health-related quality of life. In this cohort, excess mortality was associated only with the largest increase in weight, ≥ 15 kg (equivalent to BMI change >4.7 kg/m^2), despite the long follow-up time up to the average age of 73 years. At the other end, zero or negative weight change was not associated with increased mortality. In contrast, impaired quality of life in old age was directly connected with earlier weight gain. The association was strong and graded in most of the quality of life scales, and independent of both weight at 25 years of age and weight in old age. Those men who had avoided weight gain during midlife had clearly the best quality of life in old age. Even the lowest weight gain (≤4 kg) until midlife impaired HRQoL in old age, 26 years later, compared to zero weight change, with clinically meaningful (over 3 points) impairments in all of the RAND-36 scales except Physical functioning. These results are in accordance with the study of employed Finnish men and women in which BMI weakly predicted death, but was linearly correlated with subsequent work disability, [307] as well as with the parallel results from the ELSA study data [308].

The study population was born and lived their adolescence in a society that was less prosperous than today. Even in 1974 when the average age of the participants was 47 years, only 7% were obese. Recent statistics from Finland and elsewhere in the western world show that 20% to 30% of middle-aged population are obese, and an increasing proportion of population in affluent societies start gaining weight already in childhood and early adolescence. [128] In 2004 in the United States, 17% of children and adolescents were overweight.[309]

Disability-associated health and social care costs are expected to rise with the growing numbers of overweight and obese older people. [309] This is illustrated by a study using U.S. population data showing that overweight persons used more health care services and missed more days from work.[310] In a Swedish follow-up study of 60.000 participants, overweight and obesity in young adulthood were associated with a significant risk of premature disability pension later in life.[311] Cross-sectional data from a U.S. household sample indicated that the individual impact on physical HRQoL was similar for obesity, poverty, smoking and heavy drinking.[312] Early disability and subsequent impairment of quality of life in a large segment of the population causes an enormous burden to the individuals, the health

care system and society at large, jeopardizing the benefits of the favorable trend seen in other cardiovascular risk factors.

Controversies exist over whether overweight and obesity are independent cardiovascular risk factors, or whether they play through associated risk factors. In this substudy, weight gain was associated with baseline cardiovascular risk factors, (blood pressure, cholesterol, triglycerides and post-load glucose), which are in the causal pathway of the development of diabetes and cardiovascular diseases. There was no available information of risk factor levels at age of 25, but few men were overweight at that age, and less than 1% (n=11) were obese. According to earlier studies it is unlikely that elevation of other risk factors such as blood pressure, lipids or glucose would precede weight gain. [313] [153]

It is also possible that the quality of life differences are not due to weight change as such, but to other, such as psychological or genetic factors associated with it. However, the dose-response characters of the association between weight gain and several of the RAND-36 scales disputes this possibility.

11.4 CHOLESTEROL

This substudy of nearly 40 years' duration is one of the longest follow-up studies of cholesterol. The participating men were healthy and without hypolipidemic medications at baseline, and in midlife cholesterol level was not yet associated with subjective health. The results provide evidence that serum cholesterol levels in young and middle-aged men have a long-term effect not only on cardiovascular health but also on total mortality and the quality of life in old age.

Serum cholesterol predicted total mortality significantly and in a graded fashion. The men with naturally low cholesterol levels had better long-term survival and better quality of life in old age. Although original cholesterol differences had largely diminished among the old survivors, the men with cholesterol level ≤5.0 mmol/L at baseline had the best prognosis. The apparent explanation for better functioning and well-being is that there is less cardiovascular disease, especially coronary heart disease, among men with low cholesterol. The results are in accordance with current guidelines to postpone death, but also demonstrate further advantage associated with lower cholesterol in midlife.

The benefits of very low cholesterol have been disputed. The Honolulu Heart Program showed that low blood cholesterol levels predicted a greater total mortality risk in older people. [195] The explanation given for this J-shaped curve of cholesterol levels and mortality has been that fatal diseases such as cancer, for example, may lower cholesterol in the terminal stage, giving the J-shaped association if only the final years are examined. [196]

It is equally important that low cholesterol is not associated with adverse effects on mental functioning during long term. It has been debated whether low or lowered cholesterol could have a negative effect on mental or cognitive function. In a meta-analysis, Shin et al. found an inverse, non-significant association between LDL levels and depression, especially in those without lipid-lowering medication.[314] In the present substudy no such trend could be found for the mental component of quality of life; in all, the mental element was not affected.

11.5 ALCOHOL

Total alcohol consumption in Finland has doubled during the last 30 years. Subsequently, the alcohol-related morbidity and mortality have been increasing in the Finnish population. [315] Yet, due to the cardio protective effects of ethanol, light or moderate alcohol use is often recommended to enhance health. Alcohol consumption is usually a life-long habit and thus the health effects should also be considered in the long-term: the possible postponement of coronary heart disease [316] may not be worth the possible negative effects on health later on. Therefore it is relevant to consider also other outcomes in connection with alcohol intake. Total mortality and health-related quality of life in old age were chosen as outcome measures for this substudy on alcohol effects during a 29-year follow-up.

In this male population alcohol use in midlife was significantly and in a graded fashion associated with several cardiovascular risk factors. Despite this, only the highest category of consumption was related to increased mortality during the long follow-up. Even this association was not statistically significant if baseline risk factors were adjusted for. Among survivors in 2000, midlife alcohol consumption was not associated with either physical or mental quality of life. However, high consumption was harmful to HRQoL if deaths during follow-up were accounted for.

An important finding was that being an abstainer did not show any particular disadvantages on health. This suggests that moderate alcohol consumption as such may not offer special health benefits as compared to zero consumption. Taking into account the substantial harms of excessive alcohol use, these findings question the need to promote alcohol use for health reasons.

Although there are many previous studies on alcohol and mortality, this study has special strengths for studying the effects of alcohol itself. Important confounders, socioeconomic class and co-morbidity at baseline have been reduced, other cardiovascular risk factors are taken into account, the follow-up time of mortality is almost 30 years, and there is information of alcohol consumption at different time points of the follow-up with the original differences between the groups persisting.

In general, respondents tend to underreport their alcohol intake in surveys.[317] However, a more detailed history taking such as asking the amount of specific

beverages seems to result in higher reported consumption. [318] In the study cohort, the reporting of alcohol consumption is regarded reliable by the consistent pattern of consumption over the decades. The tracking of the consumption from 1974 to 2000 was good, and the reported alcohol intake was significantly correlated with several risk factors known to be associated with alcohol consumption. In addition, reported alcohol consumption was also associated with serum gamma GT, a liver function test, which can also be applied to indicate alcohol consumption [319].

An important question as to alcohol consumption is the long-term trade-off between harmful and possible beneficial effects. In this study, the long-term effects of alcohol on mortality and health were unexpectedly quite neutral. This suggests that harmful effects associated with greater alcohol consumption may in fact be due to factors other than alcohol, such as smoking, hypertension or weight gain, which cannot be distinguished in cross-sectional studies. And at the other end, these results indicate that alcohol is not needed for successful aging, and it is simultaneously possible to delay death and maintain a good quality of life without drinking moderate amounts of alcohol. Although alcohol consumption as such seemed to be less harmful when adjusted for smoking and other cardiovascular risk factors (and vice versa zero consumption was less beneficial), it can be debated whether it is applicable to adjust alcohol consumption too extensively. Alcohol use contributes to weight gain [320], high blood pressure and lipid abnormalities, and these factors are evidently in the pathogenetic trail between alcohol and adverse outcomes such as mortality. Also counting only survivors in old age can produce a bias because those who have been able to cut their drinking may be better off. Therefore, in this study also deaths were accounted for and in these analyses greater alcohol consumption had a noticeably harmful effect on HRQoL.

11.6 SMOKING

In this substudy, smoking status in middle age predicted mortality and health-related quality of life in old age in a cohort of men who were healthy and socioeconomically similar at baseline. Mortality and HRQoL showed a dose-dependent relationship to the number of daily cigarettes smoked with heavy smokers suffering the greatest loss on these end-points. In spite of the 69% cessation rate during follow-up, 44 % of those who were smoking more than 20 cigarettes daily 26 years earlier had died compared to 16% in the non-smoker group, and those who survived to the mean age of 76, had a significantly lower HRQoL than never-smokers as measured with the RAND-36 instrument. Compared to never-smokers, they had worse scores in all 8 RAND-36 scales, from 3.9 points less in Social functioning up to the overwhelming 13.8 points less in Physical functioning.

Heavy smokers had a total mortality risk that was over 2.5 fold of that of never-

smokers and over two-fold of those who had quit by 1974. This mortality rate is larger than in previous studies, but similar to that found in the British doctors' study. [239] The men smoking 11-20 cigarettes daily had a 90% higher mortality than never-smokers. However, smoking 10 cigarettes or less daily in midlife did not increase mortality in the study cohort, but the number of men in this group was small and the finding is not statistically significant. It is also possible that many men in this group were initially intermittent smokers explaining the lower mortality. Also the cessation rate during follow-up was greatest in this group: only 8% were smoking in 2000.

Those who had stopped smoking already by middle age did still have a higher mortality risk during follow-up than never smokers. It has been shown that mortality risk is reduced to the level of never smokers after 10 or more years of smoking cessation. [321] [322] In this cohort, however, the mortality risk of quitters remained 29% higher even though they had quit more than 25 years before. This unexpectedly poor outcome in spite of early cessation may imply that the men in the quitters group have formerly been heavy smokers. One might assume that those who had quit smoking had done so due to an underlying disease, but in the study cohort the participants were all healthy with no evidence of chronic diseases in 1974. However, ex-smokers did report poorer self-perceived health than never smokers already at baseline. But it is of note, that as seen in mortality, this trend persisted during the 26 year follow-up: they still reported a poorer HRQoL in 2000 in all RAND-36 scales and subsequently in the physical and mental component summary scores PCS and MCS. However these differences were not large, and cannot be compared to the overwhelming effect that long-time heavy smoking has on these endpoints.

The fact that there is no update of the changes in the participants' smoking habits between 1974 and 2000 could be regarded as a source of bias. The cessation rate during follow-up is large, but this reflects the real-life change in smoking habits of educated men from 1974 to 2000 in Finland [323] and elsewhere [246]. However, in the present study only baseline smoking status is observed in relation to the endpoints in 2000, and the number of men who took up smoking in between is very small. In fact, the high rate of cessation during follow-up is liable to have diluted some of the harmful effects of smoking in this cohort, since compared to smoking, quitting itself has been shown to be beneficial for HRQoL. [253] Cessation of smoking after baseline may be due to illness which in turn negatively affects the HRQoL, possibly showing relatively better scores for smokers in 2000. Compared to a cross-sectional setting, the longitudinal design in the present study actually helps elude the possible bias.

In 1974, the smokers reported their perceived health status to be worse than non-smokers already at baseline, assessed with the 5-step health measure. A previous study on short-range smoking and SF-36 failed to show significant differences.[324] Yet a study in a cohort of healthy Brazilian students demonstrated that the HRQoL of smokers differed already in the first years of smoking as non-smokers showed

significantly better SF-36 scores than smokers in Physical functioning, Bodily pain, General health and Vitality. [325] These differences were attributed more to the smokers' psychological profile than to tobacco itself. This would imply that those who are apt to take up smoking may have intrinsic psychological features, which are also mirrored in their quality of life before tobacco has had its effect on HRQoL. An early age of onset of smoking has been associated with a poorer health-related quality of life and reduced life satisfaction.[326] [327] Thus it is possible, that also in our cohort genetic factors, earlier life phenomena and psychological features may be reflected in the baseline differences of HRQoL between the groups.

11.7 CARDIOVASCULAR RISK PROFILE

Major coronary risk factors, particularly smoking, elevated cholesterol and blood pressure strongly predict long-term cardiovascular morbidity and mortality. [86] Since many of these risk factors are preventable, an essential question is whether risk-factor modification in the long-term increases morbidity and disability in old age by postponing death.

The results of this substudy show that low levels of cardiovascular risk factors in middle age predict lower total mortality and also better quality of life with less disability in old age, 26 years later. In line with earlier studies [245] [328] the results of this substudy indicate that by keeping cardiovascular risk factors low, it is simultaneously possible to delay death, reduce cumulative morbidity and maintain better quality of life. At the same mean age of 73 years, men with an earlier history of low levels of risk factors had fewer chronic diseases, better functioning and better HRQoL than men with high risk status. Comparison of the present RAND-36 results with Finnish population data [40] showed that the profile of the low-risk group was similar to that of 45-54-year old men in the general population. It has been estimated that each 1-point difference of the RAND-36 Physical component summary (PCS) score would mean a postponement of disability by one year. [45] Thus the three point difference seen in this study population between the low vs. high risk groups would mean a suspension of the onset of disability by three years in old age for those with favorable risk factor levels in midlife. In addition to the personal gain, delaying geriatric care by three years would reduce the financial burden on the health care system considerably. At the same time, the extended mortality data suggest that from 2000 to 2002 the total mortality is accelerating in the low risk group and that it is even larger than in the high risk group. These comparisons thus lend support to the Fries' theory of the compression of morbidity. However, the follow-up time of the cohort must be extended with regular disability measurements beyond this point to settle this issue. It is possible that low- and high-risk groups would differ

genetically or because of intrauterine conditions, [329] making prevention less feasible. However, the fact that the reported BMI at age 25 did not differ much between groups suggests that more important differences in risk factors would not have developed until midlife. Subsequently, for maximum benefit, active intervention to reduce risk factors should begin in young adulthood or midlife at the latest. Intervention started in old age may reach only a limited part of the risk factor configuration or it may occur too late. In the present cohort, intervention after the age of 70 would have left a substantial part of the population uncovered, as one fifth had already died, 75% of them from potentially preventable cardiovascular diseases and cancer. Tuomilehto et al. demonstrated that even relatively modest lifestyle modifications in midlife can effectively reduce the incidence of T2D [330] and have an impact on long term mortality [331]. Benefits of modern antihypertensive and cholesterol-lowering treatments in middle-aged individuals have been repeatedly demonstrated. [332] [333] The present results might actually reflect the success of early lifestyle modification as both high- and low-risk men had attended check-ups during the 1960's and thus received health education before 1974. Based on their reported weight at the age of 25, the increase in BMI during early midlife was significantly less in the low-risk group (1.95 kg/m^2, SD 2.13 vs. 3.64 kg/m^2, SD 2.63, P<0.0001). Probably for this reason the low-risk group had lower BMI and better glucose status and other risk factors at baseline in 1974 and they also reported better physical condition. In 2000, survivors in the low-risk group were still leaner and exercised more than did the high-risk group, but the earlier clear differences in blood pressure, cholesterol, and smoking had diminished or disappeared. This is probably due not only to selective mortality, but also to medical treatment for hypertension and hyperlipidaemia, as high risk men nevertheless reported a 1.8-fold higher prevalence of hypertension in 2000.

The advantages observed in this study do not illustrate the full beneficial potential of low cardiovascular risk. There are several features which may have diluted the effect. First, the concept of "low" and "high" risk is somewhat relative, because even in the low-risk group the levels of risk factors at baseline were far from optimal and, for example, light smoking did not exclude low-risk status (see Data and methods, Table 9). According to modern standards, the group defined as low-risk in 1974, might today actually be considered as an "intermediate-risk" group. Also, in order to be categorized as high-risk, the participant's risk factors (except post load glucose) had to be over the predetermined limits on two occasions, as described in Methods. Thus all men in the high-risk group had risk factors repeatedly, whereas men with more labile risk factor levels were included in the low risk group. Second, the long-term follow-up of the cohort leads to selection through mortality as those with higher levels of risk factors were more probable to die. Third, the differences in cardiovascular risk status were seen to attenuate between the groups with time because of medications and possible changes in lifestyle, such as smoking. And

finally, all men were from the highest socioeconomic class, which itself is a protective factor, and almost all men were also living at home with their spouses. All these factors have the tendency move the hypothesis toward null.

11.8 PSYCHOLOGICAL WELL-BEING

Psychological well-being is an important part of health-related quality of life and an essential determinant of health and social outcomes. Being a generic instrument, the ability of the RAND-36 questionnaire to examine psychological well-being is limited. Thus the purpose of this substudy was to further address the relationship between cardiovascular risk factors in midlife and mental quality of life in old age. A questionnaire examining both negative and positive affect was sent to the surviving men in 2002-2003, with questions related to depression, optimism, positive life orientation and happiness. The association of cardiovascular risk factors and mental quality of life was analyzed by comparing the men with high cardiovascular risk status with the low risk group as described in substudy V. In addition to the results presented in substudy V showing lower mortality and better physical HRQoL for the low risk group, the present study demonstrates that low cardiovascular risk in midlife is also associated with better psychological well-being in old age.

In substudy V, despite a trend, the differences in RAND-36 scales indicating the mental aspects of HRQoL between groups did not reach the 3 point limit regarded as clinically meaningful. Furthermore, the 1.8 point difference for Mental health and the 2.6 point difference for Role limitations due to mental problems were not statistically significant. The 3.1 point difference in Vitality or the 3.4 point difference in Social functioning did not reach statistical significance, either. Thus, compared to RAND-36, in spite of the conceptual overlap, the methods used in substudy VI were better able to distinguish differences in psychological well-being among the groups. Although not all variables of well-being were statistically significant, the results were consistent and significant differences were observed in dimensions related to depression and feeling of happiness. However, merely showing that positive well-being is related to good quality of life may simply reflect the absence of depressed mood. In the current analyzes the difference in the feeling of happiness between the groups prevailed after adjustment for the feeling of depression, suggesting an independent association between earlier risk profile and later psychological well-being.

These results based on a long follow-up advocate some potential pathways for the associations of cardiovascular risk factors and psychological well-being. The difference in well-being may be explained by less morbidity in old age in the low-risk group as suggested by the results in substudy V. Also, alcohol consumption was higher in the high-risk group at baseline. However, according to the results

in substudy III, moderate alcohol consumption did not affect the quality of life in the study cohort, and the inclusion of alcohol use in the multivariate analysis did not explain the difference in happiness between the groups. Irrespective of the exact underlying mechanism, the present results suggest an important extra benefit of cardiovascular prevention in men – happier older years. Because positive life orientation has been shown to protect against institutional care and mortality in individuals over 75 years of age during a 10-year follow-up, [293] the full potential of low cardiovascular risk may yet to be seen in the present study population with an average age of 76 years.

The differences between the low and high-risk groups are not large, but the results should rather be taken to support a mechanism - effect of cardiovascular risk and its sequelae also on psychological well-being. Besides, as discussed above, there are several factors, for instance features in the inclusion criteria for the low risk group as well as the SES of the cohort, which may have diluted the differences in outcome between the men with low and high risk status. Thus the effect could be expected to be more pronounced in the general public.

The socioeconomic homogeneity of the cohort is of exceptional advantage in this study examining the association of cardiovascular risk factors and psychological factors because the confounding effects of social status on psychological well-being have been minimized. Happiness as well as cardiovascular risk factors are dependent also on socioeconomic factors. [334] For example, social isolation has been shown to cause psychological distress. Also low control at work has been associated with risk of cardiovascular disease.[335] Psychological stress may increase the adoption of unhealthy choices such as smoking, alcohol consumption or sedentary lifestyle. Furthermore, psychosocial factors may have a direct effect on cardiovascular risk factors through neurohumoral activation.

11.9 LIMITATIONS

11.9.1 LIMITATIONS IN STUDY SETTINGS AND METHODS

With advancing age, non-participation or missing statements in questionnaires among the study subjects may increase. As measurements cannot be made after death and because those with poorer health are less likely to provide information, important data may be lost in end-of-life studies, favouring the group with the most deaths and missing data. [336] The 2000 questionnaire was acquired at a point when the mortality among the cohort was already considerable and significantly different between the groups. It is likely that men with less favorable risk factor status were

dropped from the analysis due to ill health, possibly weakening the negative effects of risk factors on HRQoL in these studies.

The 2002-2003 response rate in this elderly cohort was satisfactory (average 73%) and there was no significant difference between the groups. The lower response rate as compared to the survey in 2000 (response rate 90%) may be due to the aging of the cohort, but another explanation is that the 2002-2003-questionnaire was substantially expanded as compared to the 2000-questionnaire. These findings have an important future implication for the Helsinki Businessmen Study population as the cohort ages, considering that the mean age in 2003 was 76 years.

11.9.2 LIMITATIONS IN RISK FACTOR MEASUREMENTS

11.9.2.1 Weight gain

A limitation pertaining substudy I is the fact that recalled weight at 25 years of age was used. However, recalled weight has been employed in several studies and it is considered reliable. [337] [338] This is also supported by the fact that there was a relationship between weight at 25 years of age and subsequent weight. Also the validity of self-reported height and weight has been verified in earlier studies, although obese people, women more often than men, tend to underreport their weight. However, the bias resulting from this has generally been small, 0.4 BMI units for men, according to an earlier study. [339] Because the waist circumference of the participants was not recorded, some medical problems that may be associated more with central rather than general obesity may have been omitted.

11.9.2.2 Cholesterol

A limitation of substudy II was that only one baseline serum cholesterol measurement was available, and that the last cholesterol value in 2000 was based on self-report of the participants. However, the tracking of serum cholesterol in survivors was good and consistent over the years, as illustrated in Figure 2. in the original publication of substudy II. Additionally, serum cholesterol was measured in 131 men in 2003 and these levels appeared to be in accordance with the self-reported values in 2000. The proportion of men with low cholesterol (≤5.0 mmol/L) at baseline was relatively small, but this was a reality in Finland and many other western countries 40 years ago.

The cholesterol levels in old age were lower than in middle age. This trend has also been observed in the Finnish population since the 1970's, and it has been

attributed to dietary changes in the population. [199] The men were healthy at baseline, and cholesterol-lowering medication was still rarely used at the time of the 1985 survey, when only 3% of respondents reported taking these drugs. A total of 16% of men stated that they were taking cholesterol-lowering medication, mainly statins, in the 2000 survey, and this had an effect on the trend of lower cholesterol values in the 2000 questionnaire. Still, the benefits of low cholesterol in this cohort mostly reflect the effect of naturally modified low cholesterol levels, and thus the results cannot be extrapolated to the effect achieved by the use of statins, for example.

11.9.2.3 Alcohol

In population studies abstainers often include former drinkers, who have stopped drinking due to illness or psychosocial problems. This may favor the outcome of moderate drinkers compared to abstainers. [340] Thus it is a limitation, that ex-drinkers were not identified in substudy III. However, the relationship between alcohol and quality of life in old age was studied at a time point when the original differences in alcohol consumption still prevailed. Furthermore, the men with substantial problems related to alcohol use before midlife were excluded from the study, and moreover, all men were clinically healthy and working at baseline. While social class has an influence on alcohol consumption and on alcohol-related mortality, [341] the homogeneity of the study cohort diminishes the impact of this important confounding effect.

While the homogeneity of the cohort offers evident advantages in investigating the effects of alcohol *per se*, it also poses some limitations. First, the cohort consisted mainly of low to moderate middle-aged drinkers and included only a limited number of heavy drinkers. This is attributable to the fact that the men were professionally active and healthy at baseline in 1974. For this reason, also those men who had evident alcohol-related problems before middle age were not included. On the other hand, this diminishes the possible bias that could result from failure to distinguish the former heavy users in the abstainers' group.

Secondly, because the cohort represents individuals who in midlife were healthy and professionally active irrespective of their alcohol consumption habits, the results cannot be extrapolated to younger men with similar consumption. Many alcohol-related deaths occur in young age groups. [342] A 25-year follow-up study in young conscripts found a clear association between alcohol use (over 14 g/day) and risk of subsequent alcohol-related hospitalizations and deaths up to the age of 45. [343]

Another limitation is that only the amount and not the pattern of drinking was investigated. The pattern of alcohol intake has been shown to have an impact on the health outcomes. [344] Risky drinking patterns hold special health hazards even if

total consumption does not surpass the limit of risk. [345] Another issue is the effect of the type of alcohol beverages (beer, wine or liquor) consumed, the significance and exact mechanisms of which are still controversial.[346] _

11.9.2.4 SMOKING

Limitations of substudy IV include that the age at which each smoker had started smoking was not recorded. But since the majority of smokers begin smoking during adolescence, [347] [348] it can be speculated that in the present cohort many had already been smoking up to 30 years by the baseline in 1974, possibly explaining the differences in perceived health. Ideally the baseline examinations should have been made before this, but this of course was not feasible.

Estimates for smoking status are based on self report and are not validated by biological tests in this study. However, self reported data on current smoking status have been determined to have high validity when compared with measured cotine levels, [349] also in the Finnish population[350].

11.9.2.5 Risk factor profile

An important limitation affecting the interpretation of the results of substudy VI is the absence of baseline data concerning psychological well-being and depressed mood. Differences between the groups may well have existed already at that time, as low-risk men rated their physical condition and general health better than high-risk men in 1974 as presented in substudy V. These considerations do not necessarily nullify the conclusion that low cardiovascular risk is beneficial for well-being – the perspective needs to be stretched out to an earlier point during the life course. It is also possible that genetic factors and early life phenomena primarily drive both happiness and cardiovascular risk – vs. intervening factors and events during lifetime. Obviously only life-long studies can resolve this issue. In the present cohort the low cardiovascular risk in midlife was primarily determined by genetic factors and life-style, because men had no preventive drug treatment at baseline. An important background factor is weight gain up to midlife, which was significantly lower in the low-risk group. Lower weight gain predicts better HRQoL as shown in substudy I.

11.9.3 GENERALIZABILITY

All subjects were Caucasian men with high social status. This is a strength of the study because it partly removes the confounding effects of SES. Social status has a noticeable adverse influence on morbidity and mortality [307] , as well as non-participation in population surveys [351], and low socioeconomic status has been shown to decrease HRQoL. [352] But it is also a limitation as the study cohort is obviously selective: Thus, it is uncertain whether the results can be extrapolated to middle-aged men of lower socioeconomic status, or to older persons or especially to women, and furthermore, whether these results can be applied to implement health policies for the general population.

It may be regarded as a limitation that mortality and HRQoL are presented here separate of each other and therefore it is not possible to make an economic evaluation of these results. In promoting the reduction of risk factor levels on the patient level, it could also be motivating for them to be able to estimate the potential gain in disability free life years or the quality of these years associated with better risk factor status. Cost-utility analysis (CUA), for example the Quality Adjusted Life Years (QALYs) cannot be estimated directly by generic HRQoL measures such as RAND-36 alone, but a preference based measure is needed. However, correlations for SF-36 and CUAs have been demonstrated in different studies [353] [354] and with these methods QALYs could be calculated from the RAND-36 points in these studies.

12 SUMMARY AND CONCLUSIONS

Choices as regards diet, smoking and alcohol consumption seem to change life expectancy by many years. However, living longer does not necessarily mean better health or better quality of life, especially during the last years of life. Longevity may mean more years of disability and lower HRQoL during the achieved extra years: people who live longer also have more time to develop coronary heart disease or other chronic diseases causing disability and worse HRQoL. For instance, non-smokers have shown to live longer with cardiovascular disease at the end of their life. [355] On the other hand, non-smokers have been shown to live with less disability. [356] In the aging society, the functional status as well as mental well-being and social functioning during these achieved extra years is central for the aging individual as well as for the society. Can he live and enjoy life fully and independently or can he only manage by the help of others in an institution? Consequently, in addition to the more classical outcomes such as mortality and morbidity, HRQoL has become an increasingly essential end point in clinical practice and research especially in longitudinal studies measuring changes in health towards the old age.

The thesis of this study is that with favorable cardiovascular risk factor levels earlier in life, it is possible to both postpone death as well as the onset of disability and support well-being in old age. This hypothesis was examined in a cohort of men, who were healthy in middle age and were followed until the mean age of 73 years for mortality and quality of life. The results of this study indicate that lifestyle and different risk factor levels in midlife have a meaningful impact on the quality of these extra years. Leading a healthy lifestyle improves both survival and quality of life.

13 IMPLICATIONS AND FUTURE PERSPECTIVES

The impact of cardiovascular risk factors on health has been well documented. But while the risks are well known and means of effective prevention available, the implementation of preventive measures is still insufficient. There is inadequacy in early identification of risk factors, there is delay in instigating corrective measures and finally, there is failure in achieving the goals or treatment targets. For instance, in Finland, according to the National FINRISK 2007 Study, 36% of men aged 25-

34 years were smokers, 2/3 of men aged 35-64 had their cholesterol level over 5.0 mmol/L and 2/3 were overweight or obese. [129] Approximately half of Finns with diabetes are unaware of their disease status. [357]

The studies presented in this thesis substantiate that corrective measures should be started early. For instance, in substudy II the 39-year follow-up of the effect of cholesterol suggests that identifying and lowering elevated cholesterol levels should be done early in life. The substudy on smoking confirms that for maximum benefit, smoking should not be started at all. In this case the preventive effort should be aimed at teenagers. The same applies to other cardiovascular risk factors, and especially to early weight gain, considering the current obesity epidemic and the increased incidence of T2D at an early age and as signs of atherosclerosis are increasingly seen in individuals in their twenties.[358]

However, it is a common problem in primary prevention policies that persons with risk factors, but who are in a state of wellness, are not necessarily receptive to making changes in their lifestyle or motivated to start medication when they do not have any symptoms. Persons with riskier lifestyles may argue against health education and risk factor intervention by declaring that they prefer to enjoy life while they can, even if it is shorter. Estimating the quality of the potential additional years gained by preventive measures could be highly motivating for the individual's change of lifestyle. However, the argument of better quality of life in old age may be more meaningful for a person approaching the age of retirement and thus other measures must be utilized for those in young adulthood or middle-age.

It has been argued, that the risk estimators in clinical use, such as ATP-III [334] or SCORE [359], which estimate a 10 year risk of cardiovascular disease or death according to the individual's risk factor profile, may have too short a perspective, underestimating the life-time risk.[360 361] This concerns especially women, whose risk of cardiovascular disease is lower in middle-age. [120] More studies with substantial numbers of participants with adequate baseline information, followed for the whole life-span are needed to identify and illustrate the impact of risk factors on health and survival at old ages. This would mean a long-term longitudinal study started before the risk factor has had time to produce its negative health effects, and with a follow-up time long enough to enable measuring the HRQoL during "the last years" while taking also death into account. However, the risk factor status of the participants may fluctuate due to changes in lifestyle or medication during a long follow-up. Ideally, in-between measurements of risk factors are thus needed. Studies of this kind are difficult to conduct, but they are also required in order to evaluate the effect of modifiable risk factors on health in regard to the hypothesis of the compression of morbidity. [362 363]

Although the patient's well-being and quality of life have always been underlying priorities in patient care in clinical practice, only since the 1990's have HRQoL

domains been accepted as important outcome measures in medical and social research. Self-perceived physical and mental health and function are now considered valid indicators of change in intervention studies, and HRQoL assessments are acknowledged as an integral part of patient information in clinical studies. [364] The results from the studies in this thesis corroborate that by focusing on illness, important aspects of human health may be missed, and that morbidity and mortality statistics might not be a sufficient basis for setting preferences in one's lifestyle or priorities in health care policy.

The studies presented in this thesis bring new information to the usefulness of interventions for adding healthy years, rather than just additional years. These long-term results suggest that successful control of cardiovascular risk factors in middle age is associated with fewer premature deaths, greater longevity, less costs for the health care and better quality of life in old age. This advocates the implementation and motivation of lifestyle modification and cardiovascular preventive measures in middle-aged and younger people.

14 ACKNOWLEDGEMENTS

This thesis is based on the data of the Helsinki Businessmen Study, a follow-up study of originally over 3.000 men started in the 1960's and continuing to the present day. The studies were carried out at the Department of Medicine in the Helsinki University Hospital.

The "Founding Fathers" of the Helsinki Businessmen Study were Professor Tatu A. Miettinen, Professor Jussi Huttunen, Doctors Vesa Naukkarinen, Seppo Mattila and Torgeir Kumlin (deceased), as well as Professor Kalevi Pyörälä. In the beginning of the 1970's they perceived the value of the data that had been collected earlier in health examinations conducted for middle-aged businessmen at the Finnish Institute of Occupational Health. Under the leadership of Professor Miettinen, several scientific publications on various aspects of cardiovascular health in this cohort were subsequently published in high-profile international journals during the 1970's and 1980's. Also four academic dissertations (Doctors Seppo Mattila, Vesa Naukkarinen, Hannu Vanhanen and Veikko Salomaa) were produced during the 1980's. Although slumbering for some years in between, the aging study cohort was activated in 2000, when Professor Timo Strandberg with co-workers received a grant from the Sohlberg Foundation and the Helsinki University Hospital to investigate factors affecting successful aging in the Helsinki Businessmen Study. They were able to launch several projects assessing the rate and causes of functional and cognitive decline associated with aging. Ten years ago health-related quality of life (HRQoL) was yet an emerging outcome in clinical studies, and a far-sighted idea was to include measuring HRQoL in this aging cohort. I was invited in 2002 to take part in the study to investigate the associations of the risk factors these men had in their middle age on HRQoL of their older days.

Today, the Helsinki Businessmen Study stands among the most prominent longitudinal studies of successful aging. The study is ongoing, with new questionnaires dispatched to the participants every three years. In spite of the average age of 80 and the ailing health of many of the participants, the response rate has remained high, 70 % in 2007. The next survey is planned for 2010, so with the continuing help of the participants, we hope to discover many new leads to the secrets of healthy aging.

On behalf of the study group of the Helsinki Businessmen study, this thesis gives me an opportunity to express our gratitude to the participants and our respect for the dedication they have shown by meticulously filling out the many surveys we have sent them during the last ten years.

I am also deeply indebted to my principal supervisor Professor Timo Strandberg, my dear brother and mentor, for the opportunity to be able to work for this unique study. I am grateful for his invaluable guidance during the process of this thesis.

I was first introduced to the world of follow-up studies by Professor Juhani Ilmarinen in 1989. Having already worked under his guidance in an earlier project, I was fortunate to have him as the second supervisor for my thesis. I am thankful for all his support during the process.

I wish to thank Professor Reijo Tilvis for his support on the preparation of this thesis. His vast knowledge in the field of healthy aging and his often very practical advice and comments helped to clarify the manuscript substantially.

I express my gratitude to the other current members of the Helsinki Businessmen Study work group, especially to Professor emeritus Tatu A. Miettinen, as well as Professors Kaisu Pitkälä and Veikko Salomaa for their collaboration on the substudies as well as other publications during the past years. I am proudly looking forward to working with them on future studies.

I am grateful to Professor Ismo Räihä and Docent Tiina Laatikainen for their valuable time while reviewing my manuscript and the constructive criticism and suggestions which helped to strengthen the quality of this thesis.

I sincerely thank Doctor Sakari Sulosaari, MD, my friend and co-worker, with whom we have regularly discussed the impact of risk factors in every day clinical work as well as in many clinical trials over the years. His support for this thesis has been invaluable.

I wish to acknowledge Docent Markku Kallio for his enthusiasm as well as practical guidance which inspired me during the process.

I express my love and gratitude for my parents Einar and Pirkko Strandberg for all the help and encouragement they have provided me, and not just during the preparation of this thesis.

This thesis would not have been possible without the support of my family. I thank my wife Elina, and our children Viola, Joel and Juhana for creating a home with an atmosphere for discussion, expression of ideas and innovation, for science and for art.

The financial support of the Ida Montin Foundation, the Finnish Medical Foundation and the University of Helsinki is acknowledged with appreciation.

Helsinki, February 22, 2010

Arto Strandberg

15 APPENDICES

15.1 APPENDIX A: RAND 36-ITEM HEALTH SURVEY 1.0

1. In general, would you say your health is:	
Excellent	1
Very good	2
Good	3
Fair	4
Poor	5

2. **Compared to one year ago**, how would you rate your health in general **now**?	
Much better now than one year ago	1
Somewhat better now than one year ago	2
About the same	3
Somewhat worse now than one year ago	4
Much worse now than one year ago	5

The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much? **(Circle One Number on Each Line)**

	Yes, Limited a Lot	Yes, Limited a Little	No, Not limited at All
3. **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	[1]	[2]	[3]
4. **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	[1]	[2]	[3]
5. Lifting or carrying groceries	[1]	[2]	[3]
6. Climbing **several** flights of stairs	[1]	[2]	[3]
7. Climbing **one** flight of stairs	[1]	[2]	[3]
8. Bending, kneeling, or stooping	[1]	[2]	[3]
9. Walking **more than a mile**	[1]	[2]	[3]
10. Walking **several blocks**	[1]	[2]	[3]
11. Walking **one block**	[1]	[2]	[3]
12. Bathing or dressing yourself	[1]	[2]	[3]

During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of your physical health**? **(Circle One Number on Each Line)**

	Yes	No
13. Cut down the amount of time you spent on work or other activities	1	2
14. **Accomplished less** than you would like	1	2
15. Were limited in the **kind** of work or other activities	1	2
16. Had **difficulty** performing the work or other activities (for example, it took extra effort)	1	2

During the **past 4 weeks,** have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious)?
(Circle One Number on Each Line)

	Yes	No
17. Cut down the **amount of time** you spent on work or other activities	1	2
18. **Accomplished less** than you would like	1	2
19. Didn't do work or other activities as **carefully** as usual	1	2

20. During the **past 4 weeks,** to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups? **(Circle One Number)**

Not at all 1
Slightly 2
Moderately 3
Quite a bit 4
Extremely 5

21. How much **bodily** pain have you had during the **past 4 weeks**? **(Circle One Number)**

None 1
Very mild 2
Mild 3
Moderate 4
Severe 5
Very severe 6

22. During the **past 4 weeks,** how much did **pain** interfere with your normal work (including both work outside the home and housework)? **(Circle One Number)**

Not at all 1
A little bit 2
Moderately 3
Quite a bit 4
Extremely 5

These questions are about how you feel and how things have been with you **during the past 4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling.
How much of the time during the **past 4 weeks** . . . **(Circle One Number on Each Line)**

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	None of the Time
23. Did you feel full of pep?	1	2	3	4	5	6
24. Have you been a very nervous person?	1	2	3	4	5	6
25. Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
26. Have you felt calm and peaceful?	1	2	3	4	5	6
27. Did you have a lot of energy?	1	2	3	4	5	6
28. Have you felt downhearted and blue?	1	2	3	4	5	6
29. Did you feel worn out?	1	2	3	4	5	6
30. Have you been a happy person?	1	2	3	4	5	6
31. Did you feel tired?	1	2	3	4	5	6

32. During the **past 4 weeks,** how much of the time has your **physical health or emotional problems** interfered with your social activities (like visiting with friends, relatives, etc.)? **(Circle One Number)**

All of the time 1
Most of the time 2
Some of the time 3
A little of the time 4
None of the time 5

How TRUE or FALSE is each of the following statements for you. **(Circle One Number on Each Line)**

	Definitely True	Mostly True	Don't Know	Mostly False	Definitely False
33. I seem to get sick a little easier than other people	1	2	3	4	5
34. I am as healthy as anybody I know	1	2	3	4	5
35. I expect my health to get worse	1	2	3	4	5
36. My health is excellent	1	2	3	4	5

15.2 APPENDIX B: RAND 36-ITEM HEALTH SURVEY 1.0 IN FINNISH. RAND-36 ELÄMÄNLAADUN KYSELY, SUOMENKIELINEN VERSIO (STAKES/KTL)

1. Onko terveytenne yleisesti ottaen **(ympyröikää yksi vaihtoehto)**	
Erinomainen	1
Varsin hyvä	2
Hyvä	3
Tyydyttävä	4
Huono	5

2. Jos vertaatte terveydentilaanne vuoden takaiseen, onko terveytenne yleisesti ottaen **(ympyröikää yksi vaihtoehto)**	
Tällä hetkellä paljon parempi kuin vuosi sitten	1
Tällä hetkellä jonkin verran parempi kuin vuosi sitten	2
Suunnilleen samanlainen	3
Tällä hetkellä jonkin verran huonompi kuin vuosi sitten	4
Tällä hetkellä paljon huonompi kuin vuosi sitten	5

Seuraavassa luetellaan erilaisia päivittäisiä toimintoja. Rajoittaako terveydentilanne nykyisin suoriutumistanne seuraavista päivittäisistä toiminnoista? Jos rajoittaa, kuinka paljon? **(ympyröikää yksi numero joka riviltä)**

	Kyllä, rajoittaa paljon	Kyllä, rajoittaa hiukan	Ei rajoita lainkaan
3. Huomattavia ponnistuksia vaativat toiminnat (esimerkiksi juokseminen, raskaiden tavaroiden nostelu, rasittava urheilu)	[1]	[2]	[3]
4. Kohtuullisia ponnistuksia vaativat toiminnat kuten pöydän siirtäminen, imurointi, keilailu	[1]	[2]	[3]
5. ruokakassien nostaminen tai kantaminen	[1]	[2]	[3]
6. nouseminen portaita useita kerroksia	[1]	[2]	[3]
7. nouseminen portaita yhden kerroksen	[1]	[2]	[3]
8. vartalon taivuttaminen, polvistuminen, kumartuminen	[1]	[2]	[3]
9. noin kahden kilometrin matkan kävely	[1]	[2]	[3]
10. noin puolen kilometrin matkan kävely	[1]	[2]	[3]
11. noin 100 metrin matkan kävely	[1]	[2]	[3]
12. kylpeminen tai pukeutuminen	[1]	[2]	[3]

Onko Teillä viimeisen 4 viikon aikana ollut ruumiillisen terveydentilanne takia alla **mainittuja ongelmia tavanomaisissa päivittäisissä tehtävissänne? (ympyröikää yksi numero joka riviltä)**

	Kyllä	Ei
13. Vähensitte työhön tai muihin tehtäviin käyttämäänne aikaa	1	2
14. Saitte aikaiseksi vähemmän kuin halusitte	1	2
15. Terveydentilanne asetti teille rajoituksia joissakin työ- tai muissa tehtävissä	1	2
16. Töistänne tai tehtävistänne suoriutuminen tuotti vaikeuksia (olette joutunut esim. ponnistelemaan tavallista enemmän)	1	2

Onko Teillä viimeisen 4 viikon aikana ollut tunne-elämään liittyvien vaikeuksien (esim. masentuneisuus tai ahdistuneisuus) takia alla mainittuja ongelmia työssänne tai muissa tavanomaisissa päivittäisissä tehtävissänne? **(ympyröikää yksi numero joka riviltä)**

	Yes	No
17. Vähensitte työhön tai muihin tehtäviin käyttämäänne aikaa	1	2
18. Saitte aikaiseksi vähemmän kuin halusitte	1	2
19. Ette suorittanut töitänne tai muita tehtäviänne yhtä huolellisesti kuin tavallisesti	1	2

20. Missä määrin ruumiillinen terveydentilanne tai tunne-elämän vaikeudet ovat viimeisen 4 viikon aikana häirinneet tavanomaista (sosiaalista) toimintaanne perheen, ystävien, naapureiden tai muiden ihmisten parissa? (ympyröikää yksi vaihtoehto)

ei lainkaan 1
hieman 2
kohtalaisesti 3
melko paljon 4
erittäin paljon 5

21. Kuinka voimakkaita ruumiillisia kipuja Teillä on ollut viimeisen 4 viikon aikana? **(ympyröikää yksi vaihtoehto)**

ei lainkaan	1
hyvin lieviä	2
lieviä	3
kohtalaisia	4
voimakkaita	5
erittäin voimakkaita	6

22. Kuinka paljon kipu on häirinnyt tavanomaista toimintaanne (kotona tai kodin ulkopuolella) viimeisen 4 viikon aikana? **(ympyröikää yksi vaihtoehto)**

ei lainkaan	1
hieman	2
kohtalaisesti	3
melko paljon	4
erittäin paljon	5

Seuraavat kysymykset koskevat sitä, miltä Teistä on tuntunut viimeisen 4 viikon aikana. Merkitkää kunkin kysymyksen kohdalla se numero, joka parhaiten kuvaa tuntemuksianne.

Kuinka suuren osan ajasta olette viimeisen 4 viikon aikana ... **(ympyröikää yksi vaihtoehto)**

	Koko ajan	Suurimman osan aikaa	Huomattavan osan aikaa	Jonkin aikaa	Vähän aikaa	En lainkaan
23. tuntenut olevanne täynnä elinvoimaa	1	2	3	4	5	6
24. ollut hyvin hermostunut	1	2	3	4	5	6
25. tuntenut mielialanne niin matalaksi, ettei mikään ole voinut teitä piristää	1	2	3	4	5	6
26. tuntenut itsenne tyyneksi ja rauhalliseksi	1	2	3	4	5	6
27. ollut täynnä tarmoa	1	2	3	4	5	6
28. tuntenut itsenne alakuloiseksi ja apeaksi	1	2	3	4	5	6
29. tuntenut itsenne ”loppuun-kuluneeksi”	1	2	3	4	5	6
30. ollut onnellinen	1	2	3	4	5	6
31. tuntenut itsenne väsyneeksi	1	2	3	4	5	6

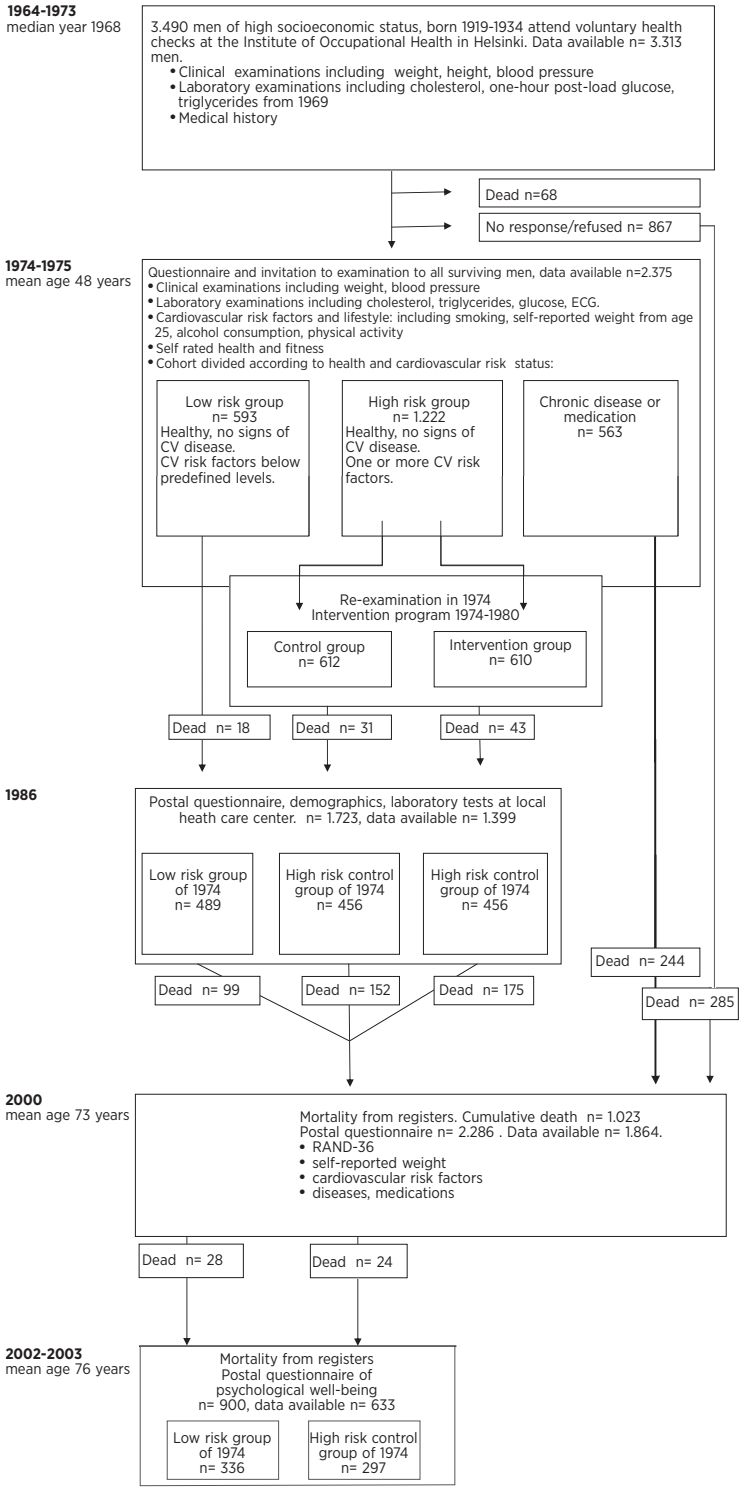
32. Kuinka suuren osan ajasta ruumiillinen terveydentilanne tai tunne-elämänvaikeudet ovat viimeisen 4 viikon aikana häirinneet tavanomaista sosiaalista toimintaanne (ystävien, sukulaisten, muiden ihmisten tapaaminen)? **(ympyröikää yksi vaihtoehto)**

koko ajan	1
suurimman osan aikaa	2
jonkin aikaa	3
vähän aikaa	4
ei lainkaan	5

Kuinka hyvin seuraavat väittämät pitävät paikkansa Teidän kohdallanne? **(ympyröikää yksi vaihtoehto)**

	Pitää ehdottomasti paikkansa	Pitää enimmäkseen paikkansa	En osaa sanoa	Enimmäkseen ei pidä paikkaansa	Ehdottomasti ei pidä paikkaansa
33. Minusta tuntuu, että sairastun jonkin verran helpommin kuin muut ihmiset	1	2	3	4	5
34. Olen vähintään yhtä terve kuin kaikki muutkin tuntemani ihmiset	1	2	3	4	5
35. Uskon, että terveyteni tulee heikkenemään	1	2	3	4	5
36. Terveyteni on erinomainen	1	2	3	4	5

15.3 APPENDIX C: THE HELSINKI BUSINESSMEN STUDY TIMELINE



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